AZOLE METHYLIDENE CYANIDE DERIVATIVES AND THEIR USE AS PROTEIN KINASE MODULATORS

Field of the invention

The present invention is related to novel azole methylidene cyanide derivatives and their tautomers, as well as pharmaceutical compositions containing such azole derivatives. In particular, the present invention is related to the modulation, notably the inhibition of the protein kinase pathway by using azole methylidene cyanide derivatives of the present invention. Preferred protein kinases are c-Jun N-terminal kinase (JNK) and Glycogen Synthase Kinase 3 (GSK3). The compounds of the present invention are particularly useful in the treatment of neurodegenerative diseases, neuronal disorders, inflammatory diseases, cardiovascular diseases, cancer or metabolic disorders mediated by insulin resistance or hyperglycemia, comprising diabetes type I and/or II, inadequate glucose tolerance, insulin resistance, obesity, polycystic ovary syndrome (PCOS). The present invention is furthermore related methods for the preparation of the novel azole methylidene cyanide derivatives.

Background of the invention

Cellular signaling has become a major research theme in biology and medicine over the past twenty years. The complex pathways and protein components in signal transduction are emerging with increasing clarity. Over the last 15 years, the protein kinases, such as the protein tyrosine kinases, have been identified as key players in cellular regulation. They are involved in immune, endocrine, and nervous system physiology and pathology and thought to be important in the development of many cancers. As such they serve as drug targets for many different diseases. Members of protein kinase family include for example c-Jun N-terminal kinase or Glycogen Synthase Kinase 3 (GSK3).

C-Jun N-Terminal kinase (JNK) is a member of the MAP Kinase family that includes the extracellular regulated kinases (ERKs) and p38 kinases. It is a serine/threonine kinase that phosphorylates c-Jun, a transcription factor activator protein-1 (AP-1) component. AP-1 regulates the transcription of several genes including inflammatory enzymes (COX-2), matrix metalloproteinases (MMP-13), cytokines (TNF), growth factors (VEGF) and immunoglobulins. Three JNK isoforms, JNK-1, -2 and –3, have been identified in humans and they appear to mediate critical phosphorylation events involved in the regulation of apoptosis and the immune response.

In a publication of Xie X et al, (*Structure* **6 (8)** p.983-991 (1998)) it has been suggested that activation of stress-activated signal transduction pathways are required for neuronal apoptosis induced by NGF withdrawal in rat PC-12 and superior cervical ganglia (SCG) sympathetic neuronal cells. Inhibition of specific kinases, namely MAP kinase kinase 3 (MKK3) and MAP kinase kinase 4 (MKK4), or c-Jun (part of the MKK-4 cascade) may be sufficient to block apoptosis (see also Kumagae Y et al, in *Brain Res*, **67(1)**, 10-17 (1999) and Yang DD et al in *Nature*, **389** p.865-870 (1997)).

It has been reported that the JNK signalling pathway is implicated in cell proliferation and could play an important role in autoimmune diseases (Yang et al, *Immunity* **9**, 575-585 (1998); Sabapathy et al. *Current Biology* **3**, 116-125 (1999)) which are mediated by T-cell activation and proliferation.

One of the first compounds that inhibits the JNK pathway is Cephalon's CEP-1347 which was found to be neuroprotective in a number of *in vivo* models of neurodegenerative disease. Several compounds are reported in the patent literature to inhibit JNKs. Hoffmann-La Roche claimed 4-heteroaryl, 4-arylindolinones and annulated indolinones (WO 0035921, WO 0035909 and WO 0035906). Vertex Pharmaceuticals disclosed oxime derivatives as a JNK3 inhibitor (WO0064872). Applied Research Systems has disclosed benzazole derivatives (EP 1110957) as JNK inhibitors.

Glycogen synthase kinase 3 (GSK3) is a serine/threonine kinase for which two isoforms, α and β, have been identified (Woodgett et al. *Trends Biochem. Sci.*, **16** p.177-81 (1991)). Both GSK3 isoforms are constitutively active in resting cells. GSK3 was originally identified as a kinase that inhibits glycogen synthase by direct phosphorylation. Upon insulin activation, GSK3 is inactivated, thereby allowing the activation of glycogen synthase and possibly other insulin-dependent events, such glucose transport. Subsequently, it has been shown that GSK3 activity is also inactivated by other growth factors that, like insulin, signal through receptor tyrosine kinases (RTKs). Examples of such signalling molecules include IGF-1 and EGF (Saito et al. *Biochem. J.*, **303** p.27-31 (1994), Welsh et al., *Biochem. J.*, **294** p.625-29 (1993) and Cross et al., *Biochem. J.*, **303** p.21-26 (1994)). GSK3 beta activity is regulated by serine (inhibitory) and tyrosine (stimulatory) phosphorylation, by protein complex formation, and by its intracellular localization. GSK3 beta phosphorylates and thereby regulates the functions of many metabolic, signalling and structural proteins (Carol Grimes, Richard Jope, *Prog. Neurobiol.* **65(4)** p.391-426 (2001)). Notable among the signalling proteins regulated by GSK3 beta are the many transcription factors, including activator protein-1 cells, Myc, beta-catenin, CCAAT/enhancer binding protein, and NFkappaB.

Agents that inhibit GSK3 activity are useful in the treatment of disorders that are mediated by GSK3 activity. In addition, inhibition of GSK3 mimics the activation of growth factor signalling pathways and consequently GSK3 inhibitors are useful in the treatment of diseases in which such pathways are insufficiently active. Examples of diseases that can be treated with GSK3 inhibitors, such as diabetes, neurodegenerative diseases (e.g. Alzheimer's disease), inflammatory diseases, ischemia and cancer are described below.

In the patent literature, several GSK3 inhibitors have already been disclosed (WO 02/20495, Chiron Corporation; WO 02/10141, Pfizer Products Inc.; WO 02/22608, Vertex Pharmaceuticals Inc.).

Diabetes mellitus is a serious metabolic disease that is defined by the presence of chemically elevated levels of blood glucose (hyperglycemia). The term diabetes mellitus encompasses several different hyperglycemic states. These states include Type 1 (insulin-dependent diabetes mellitus or IDDM) and Type 2 (non-insulin dependent diabetes mellitus or NIDDM) diabetes. The hyperglycemia present in individuals with Type 1 diabetes is associated with deficient, reduced, or nonexistent levels of insulin that are insufficient to maintain blood glucose levels within the physiological range. Conventionally, Type 1 diabetes is treated by administration of replacement doses of insulin, generally by a parenteral route.

Type 2 diabetes is an increasingly prevalent disease of aging. It is initially characterized by decreased sensitivity to insulin and a compensatory elevation in circulating insulin concentrations, the latter of which is required to maintain normal blood glucose levels. As described above, GSK3 inhibition stimulates insulin-dependent processes and is consequently useful in the treatment of type 2 diabetes. Recent data obtained using lithium salts provides evidence for this notion. The lithium ion has recently been reported to inhibit GSK3 activity (Peter Klein, Douglas Melton *PNAS* **93** p.8455-9 (1996)). However, lithium has not been widely accepted for use in the inhibition of GSK3 activity, possibly because of its documented effects on molecular targets other than GSK3. The purine analog 5-iodotubercidin, also a GSK3 inhibitor, likewise stimulates glycogen synthesis and antagonizes inactivation of glycogen synthase by glucagon and vasopressin in rat liver cells (Fluckiger-Isler et al., *Biochem. J.* **292** p.85-91 (1993) and Massillon et al., *Biochem. J.* **299** p.123-8 (1994)). However, this compound has also been shown to inhibit other serine/threonine and tyrosine kinases (*Biochem. J.* **299** p.123-8 (1994)).

GSK3 is also involved in biological pathways relating to Alzheimer's disease (AD). The characteristic pathological features of AD are extracellular plaques of an abnormally processed form of the amyloid precursor protein (APP), so-called β-amyloid peptide (β-AP) and the development of intracellular neurofibrillary tangles containing paired

helical filaments (PHF) that consists largely of hyperphosphorylated tau protein. GSK3 is one of a number of a number of kinases that have been found to phosphorylate tau protein in vitro on the abnormal sites characteristic of PHF tau, and is the only kinase also demonstrated to do this in living cells and in animals (Lovestone et al., *Current Biology* **4** p.1077-86 (1994) and Brownlees et al., *Neuroreport* **8** p.3251-55 (1997)). Furthermore, the GSK3 kinase inhibitor, LiCl, blocks tau hyperphosphorylation in cells (Stambolic et al., *Current Biology* **6** p.1664-8 (1996)). Thus GSK3 activity may contribute to the generation of neurofibrillary tangles and consequently to disease progression. Recently it has been shown that GSK3b associates with another key protein in AD pathogenesis, presenillin 1 (PS1) (Takashima et al., *PNAS* **95** p.9637-41 (1998)). Mutations in the PS1 gene lead to increased production of β–AP, but the authors also demonstrate that the mutant PS1 proteins bind more tightly to GSK3β and potentiate the phosphorylation of tau, which is bound to the same region of PS1. Interestingly it has also been shown that another GSK3 substrate, β-catenin, binds to PS1 (Zhang et al., *Nature* **395** p.698-702 (1998)). Cytosolic β-catenin is targeted for degradation upon phosphorylation by GSK3 and reduced β-catenin activity is associated with increased sensitivity of neuronal cells to β-AP induced neuronal apoptosis. Consequently, increased association of GSK3β with mutant PS1 may account for the reduced levels of β-catenin that have been observed in the brains of PS1-mutant AD patients and to the disease related increase in neuronal cell-death. Consistent with these observations, it has been shown that injection of GSK3 antisense but not sense, blocks the pathological effects of β-AP on neurons in vitro, resulting in a 24hr delay in the onset of cell death (Takashima et al., *PNAS* **90** p.7789-93 (1993)). In these latter studies, the effects on cell-death are preceded (within 3-6 hours of β-AP administration) by a doubling of intracellular GSK3 activity, suggesting that genetic mechanisms may increase GSK3 activity. Further evidence for a role for GSK3 in AD is provided by the observation that the protein expression level (but, in this case , not specific activity) of GSK3 is increased by 50% in postsynaptosomal supernatants of AD vs. normal brain tissue

(Pei et al., *J. Neuropathol. Exp.***56** p.70-78 (1997)). Thus, it is believed that specific inhibitors of GSK3 will act to slow the progression of Alzheimer's Disease.

It has also been described an involvement of GSK3 activity in the etiology of bipolar disorder. In support of this notion it was recently shown that valproate, another drug commonly used in the treatment of said disease, is also a GSK3 inhibitor (Chen et al. *J. Neurochemistry* **72** p.1327-30 (1999)). One mechanism by which lithium and other GSK3 inhibitors may act to treat bipolar disorder is to increase the survival of neurons subjected to aberrantly high levels of excitation induced by the neurotransmitter, glutamate (Nonaka et al, *PNAS* **95** p.2642-47 (1998).

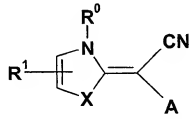
Glutamate-induced neuronal excitotoxicity is also believed to be a major cause of neurodegeneration associated with acute damage such as in cerebral ischemia, traumatic brain injury and bacterial infection. Furthermore, it is believed that excessive glutamate signalling is a factor in the chronic neuronal damage seen in diseases such as Alzheimer's, Huntingdon's, Parkinson's, AIDS associated dementia, amyotrophic lateral sclerosis (AML) and multiple sclerosis (MS) (Thomas et al., *J. Am. Geriatr. Soc.* **43** p.1279-89 (1995)). Consequently, GSK3 inhibitors are believed to be a useful treatment in these and other neurodegenerative disorders.

Sasaki et al. disclosed that GSK3 beta may have a role in ischemic neuronal cell death (Sasaki C. et al., *Neurol. Res.* **23(6)** p.588-92 (2001). Cross et al. described selective small-molecule inhibitors of glycogen synthase kinase-3 activity protecting primary neurones from death (Cross et al., *Journal of Neurochemistry* 77 p.94-102 (2001)).

It has also been reported that debromohymenialdisine (DBH), considered as inhibitors of GSK3, exhibit anti-inflammatory activity in a model of adjuvant-induced arthritis in the rat. (A. Ali et al., *American Chemical Society* p. A-N (December 2000)).

Summary of the invention

The present invention relates to new azole methylidene cyanide derivatives of formula (I)



(I)

their pharmaceutically acceptable salts, as well as use thereof for the preparation of pharmaceutical compositions in the treatment and/or prevention of neuronal disorders, neurodegenerative diseases, cardiovascular diseases, inflammatory diseases, metabolic disorders, cancer or metabolic disorders mediated by insulin resistance or hyperglycemia, comprising diabetes type I and/or II, inadequate glucose tolerance, insulin resistance, obesity, polycystic ovary syndrome (PCOS). Compounds of this invention are inhibitors of the protein kinases

Description of the invention

It has now been found that compounds of the present invention are modulators of protein kinases, particularly of the c-Jun N-terminal kinases, and Glycogen Synthase Kinase 3 (GSK3). When the protein kinase is bound by the compounds of the present invention, said kinase is inhibited by being blocked from its substrate and thus being unable to exert its biological or pharmacological effects. The compounds of the present invention are therefore useful for example in the treatment and/or prevention of neuronal disorders, neurodegenerative diseases, cardiovascular diseases, inflammatory diseases, cancer or metabolic disorders mediated by insulin resistance or hyperglycemia, comprising diabetes type I and/or II, inadequate glucose tolerance, insulin resistance, obesity, polycystic ovary syndrome (PCOS).

In particular, compounds of the present invention are useful in the treatment and prevention of protein kinases, particularly c-Jun kinases N-terminal and Glycogen Synthase Kinase 3 related disorders of mammals and especially humans.

The following paragraphs provide definitions of the various chemical moieties that make up the compounds according to the invention and are intended to apply uniformly throughout the specification and claims unless an otherwise expressly set out definition provides a broader definition.

"C_1-C_6-alkyl" refers to monovalent alkyl groups having 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl, n-hexyl and the like.

"Aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (*e.g.*, phenyl) or multiple condensed rings (*e.g.*, naphthyl). Preferred aryl include phenyl, naphthyl, phenantrenyl and the like.

"C_1-C_6-alkyl aryl" refers to C_1-C_6-alkyl groups having an aryl substituent, including benzyl, phenethyl and the like.

"Heteroaryl" refers to a monocyclic heteroaromatic, or a bicyclic or a tricyclic fused-ring heteroaromatic group. Particular examples of heteroaromatic groups include optionally substituted pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,1,3,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, 3H-indolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, quinolizinyl, quinazolinyl, pthalazinyl, quinoxalinyl, cinnolinyl, napthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolyl, isoquinolyl, tetrazolyl, 5,6,7,8-tetrahydroquinolyl, 5,6,7,8-tetrahydroisoquinolyl, purinyl, pteridinyl, carbazolyl, xanthenyl or benzoquinolyl.

"C_1-C_6-alkyl heteroaryl" refers to C_1-C_6-alkyl groups having a heteroaryl substituent, including 2-furylmethyl, 2-thienylmethyl, 2-(1H-indol-3-yl)ethyl and the like.

"C_2-C_6-alkenyl" refers to alkenyl groups preferably having from 2 to 6 carbon atoms and having at least 1 or 2 sites of alkenyl unsaturation. Preferable alkenyl groups include ethenyl (-CH=CH_2), n-2-propenyl (allyl, -CH_2CH=CH_2) and the like.

"C_2-C_6-alkenyl aryl" refers to C_2-C_6-alkenyl groups having an aryl substituent, including 2-phenylvinyl and the like.

"C_2-C_6-alkenyl heteroaryl" refers to C_2-C_6-alkenyl groups having a heteroaryl substituent, including 2-(3-pyridinyl)vinyl and the like.

"C_2-C_6-alkynyl" refers to alkynyl groups preferably having from 2 to 6 carbon atoms and having at least 1-2 sites of alkynyl unsaturation, preferred alkynyl groups include ethynyl (-C≡CH), propargyl (-CH_2C≡CH), and the like.

"C_2-C_6-alkynyl aryl" refers to C_2-C_6-alkynyl groups having an aryl substituent, including phenylethynyl and the like.

"C_2-C_6-alkynyl heteroaryl" refers to C_2-C_6-alkynyl groups having a heteroaryl substituent, including 2-thienylethynyl and the like.

"C_3-C_8-cycloalkyl" refers to a saturated carbocyclic group of from 3 to 8 carbon atoms having a single ring (*e.g.*, cyclohexyl) or multiple condensed rings (*e.g.*, norbornyl). Preferred cycloalkyl include cyclopentyl, cyclohexyl, norbornyl and the like.

"C_1-C_6-alkyl cycloalkyl" refers to C_1-C_6-alkyl groups having a cycloalkyl substituent, including cyclohexylmethyl, cyclopentylpropyl, and the like.

"heterocycloalkyl" refers to a C_3-C_8-cycloalkyl group according to the definition above, in which 1 to 3 carbon atoms are replaced by heteroatoms chosen from the group consisting of

O, S, NR, R being defined as hydrogen or C_1-C_6 alkyl. Preferred heterocycloalkyl include pyrrolidine, piperidine, piperazine, 1-methylpiperazine, morpholine, and the like.

"C_1-C_6-alkyl heterocycloalkyl" refers to C_1-C_6-alkyl groups having a heterocycloalkyl substituent, including 2-(1-pyrrolidinyl)ethyl, 4-morpholinylmethyl, (1-methyl-4-piperidinyl)methyl and the like.

"Carboxy" refers to the group –C(O)OH.

"C_1-C_6-alkyl carboxy" refers to C_1-C_6-alkyl groups having a carboxy substituent, including 2-carboxyethyl and the like.

"Acyl" refers to the group –C(O)R where R includes H, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", heterocycloalkyl"heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl acyl" refers to C_1-C_6-alkyl groups having an acyl substituent, including 2-acetylethyl and the like.

"Aryl acyl" refers to aryl groups having an acyl substituent, including 2-acetylphenyl and the like.

"Heteroaryl acyl" refers to hetereoaryl groups having an acyl substituent, including 2-acetylpyridyl and the like.

"C_3-C_8-(hetero)cycloalkyl acyl" refers to 3 to 8 membered cycloalkyl or heterocycloalkyl groups having an acyl substituent.

"Acyloxy" refers to the group –OC(O)R where R includes H, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl",

"C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl acyloxy" refers to C_1-C_6-alkyl groups having an acyloxy substituent, including 2-(acetyloxy)ethyl and the like.

"Alkoxy" refers to the group –O-R where R includes "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl alkoxy" refers to C_1-C_6-alkyl groups having an alkoxy substituent, including 2-ethoxyethyl and the like.

"Alkoxycarbonyl" refers to the group –C(O)OR where R includes "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl alkoxycarbonyl" refers to C_1-C_6-alkyl groups having an alkoxycarbonyl substituent, including 2-(benzyloxycarbonyl)ethyl and the like.

"Aminocarbonyl" refers to the group –C(O)NRR' where each R, R' includes independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl aminocarbonyl" refers to C_1-C_6-alkyl groups having an aminocarbonyl substituent, including 2-(dimethylaminocarbonyl)ethyl and the like.

"Acylamino" refers to the group –NRC(O)R' where each R, R' is independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl acylamino" refers to C_1-C_6-alkyl groups having an acylamino substituent, including 2-(propionylamino)ethyl and the like.

"Ureido" refers to the group –NRC(O)NR'R" where each R, R', R" is independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl", and where R' and R", together with the nitrogen atom to which they are attached, can optionally form a 3-8-membered heterocycloalkyl ring.

"C_1-C_6-alkyl ureido" refers to C_1-C_6-alkyl groups having an ureido substituent, including 2-(*N*'-methylureido)ethyl and the like.

"Carbamate" refers to the group –NRC(O)OR' where each R, R' is independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"Amino" refers to the group –NRR' where each R, R' is independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl",

"heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl", and where R and R', together with the nitrogen atom to which they are attached, can optionally form a 3-8-membered heterocycloalkyl ring.

"C_1-C_6-alkyl amino" refers to C_1-C_6-alkyl groups having an amino substituent, including 2-(1-pyrrolidinyl)ethyl and the like.

"Ammonium" refers to a positively charged group $-N^+RR'R''$, where each R, R',R'' is independently, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl", and where R and R', together with the nitrogen atom to which they are attached, can optionally form a 3-8-membered heterocycloalkyl ring.

"C_1-C_6-alkyl ammonium" refers to C_1-C_6-alkyl groups having an ammonium substituent, including 2-(1-pyrrolidinyl)ethyl and the like.

"Halogen" refers to fluoro, chloro, bromo and iodo atoms.

"Sulfonyloxy" refers to a group $-OSO_2$-R wherein R is selected from H, "C_1-C_6-alkyl", "C_1-C_6-alkyl" substituted with halogens, *e.g.*, an $-OSO_2$-CF_3 group, "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl sulfonyloxy" refers to C_1-C_6-alkyl groups having a sulfonyloxy substituent, including 2-(methylsulfonyloxy)ethyl and the like.

"Sulfonyl" refers to group "–SO_2-R" wherein R is selected from H, "aryl", "heteroaryl", "C_1-C_6-alkyl", "C_1-C_6-alkyl" substituted with halogens, *e.g.*, an –SO_2-CF_3 group, "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl sulfonyl" refers to C_1-C_6-alkyl groups having a sulfonyl substituent, including 2-(methylsulfonyl)ethyl and the like.

"Sulfinyl" refers to a group "–S(O)-R" wherein R is selected from H, "C_1-C_6-alkyl", "C_1-C_6-alkyl" substituted with halogens, *e.g.*, an –SO-CF_3 group, "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl sulfinyl" refers to C_1-C_6-alkyl groups having a sulfinyl substituent, including 2-(methylsulfinyl)ethyl and the like.

"Sulfanyl" refers to groups –S-R where R includes H, "C_1-C_6-alkyl", "C_1-C_6-alkyl" substituted with halogens, *e.g.*, an –SO-CF_3 group, "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl". Preferred sulfanyl groups include methylsulfanyl, ethylsulfanyl, and the like.

"C_1-C_6-alkyl sulfanyl" refers to C_1-C_6-alkyl groups having a sulfanyl substituent, including 2-(ethylsulfanyl)ethyl and the like.

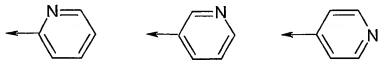
"Sulfonylamino" refers to a group $-NRSO_2-R'$ where each R, R' includes independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl sulfonylamino" refers to C_1-C_6-alkyl groups having a sulfonylamino substituent, including 2-(ethylsulfonylamino)ethyl and the like.

"Aminosulfonyl" refers to a group $-SO_2-NRR'$ where each R, R' includes independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl aminosulfonyl" refers to C_1-C_6-alkyl groups having an aminosulfonyl substituent, including 2-(cyclohexylaminosulfonyl)ethyl and the like.

"2-pyridyl, 3-pyridyl, 4-pyridyl" refers to pyridyl moieties of the following structure :



2-pyridyl 3-pyridyl 4-pyridyl

"Substituted or unsubstituted" : Unless otherwise constrained by the definition of the individual substituent, the above set out groups, like "alkyl", "alkenyl", "alkynyl", "aryl" and "heteroaryl" etc. groups can optionally be substituted with from 1 to 5 substituents selected from the group consisting of "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "cycloalkyl", "heterocycloalkyl", "C_1-C_6-alkyl aryl", "C_1-C_6-alkyl heteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl", "amino", "ammonium", "acyl", "acyloxy", "acylamino", "aminocarbonyl", "alkoxycarbonyl", "ureido", "carbamate",

"aryl", "heteroaryl", "sulfinyl", "sulfonyl", "alkoxy", "sulfanyl", "halogen", "carboxy", trihalomethyl, cyano, hydroxy, mercapto, nitro, and the like. Alternatively said substitution could also comprise situations where neighbouring substituents have undergone ring closure, notably when vicinal functional substituents are involved, thus forming, *e.g.*, lactams, lactons, cyclic anhydrides, but also acetals, thioacetals, aminals formed by ring closure for instance in an effort to obtain a protective group.

"Pharmaceutically acceptable salts or complexes" refers to salts or complexes of the below-identified compounds of formulae (I), (Ia) and (Ib) that retain the desired biological activity. Examples of such salts include, but are not restricted to acid addition salts formed with inorganic acids (*e.g.* hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, fumaric acid, maleic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene sulfonic acid, naphthalene disulfonic acid, methanesulfonic acid and poly-galacturonic acid. Said compounds can also be administered as pharmaceutically acceptable quaternary salts known by a person skilled in the art, which specifically include the quarternary ammonium salt of the formula $-NR,R',R''^{+}Z^{-}$, wherein R, R', R" is independently hydrogen, alkyl, or benzyl, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkyl aryl, C_1-C_6-alkyl heteroaryl, cycloalkyl, heterocycloalkyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, fumarate, citrate, tartrate, ascorbate, cinnamoate, mandeloate, and diphenylacetate).

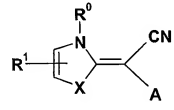
"Pharmaceutically active derivative" refers to any compound that upon administration to the recipient, is capable of providing directly or indirectly, the activity disclosed herein.

"Enantiomeric excess" (ee) refers to the products that are obtained by an asymmetric synthesis, i.e. a synthesis involving non-racemic starting materials and/or reagents or a syn-

thesis comprising at least one enantioselective step, whereby a surplus of one enantiomer in the order of at least about 52% ee is yielded.

Said formula also comprises its tautomers, its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts thereof. Preferred pharmaceutically acceptable salts of the formula (I) are acid addition salts formed with pharmaceutically acceptable acids like hydrochloride, hydrobromide, sulfate or bisulfate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulfonate, benzenesulfonate, and *para*-toluenesulfonate salts.

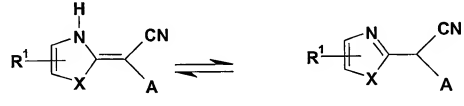
A first aspect of the invention consists in new azole methylidene cyanide derivatives of formula I



(I)

as well as its tautomers, its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms and pharmaceutically acceptable salts thereof.

Where R^0 is H, such tautomers undergo transformation in solution and an equilibrium between azole derivatives of formula (IA) is established with those of formula (IB).



(IA) (IB)

Said tautomers are comprised by the present invention.

The substituents within formula (I) are defined as follows:

X is O, S or NR^0, with R^0 being as defined below. More preferred compounds are 1,3-thiazoles, i.e. compounds of formula (I) wherein X is S.

A is an unsubstituted or substituted 2-pyridyl, 3-pyridyl, 4-pyridyl, an unsubstituted or substituted pyridazinyl, an unsubstituted or substituted pyrimidinyl, an unsubstituted or substituted pyrazinyl or an unsubstituted or substituted triazinyl group, each of the above-mentioned groups may be fused with an aryl or a heteroaryl group. Preferably, A is an unsubstituted or substituted pyrimidinyl group.

Each of said heterocyclic groups A may be substituted by at least one, preferably one, moiety R^2.

R^2 is selected from the group comprising or consisting of hydrogen, sulfonyl, amino, unsubstituted or substituted C_1-C_6-alkyl, unsubstituted or substituted C_2-C_6-alkenyl, unsubstituted or substituted C_2-C_6-alkynyl or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted saturated or unsaturated 3-8-membered cycloalkyl, unsubstituted or substituted heterocycloalkyl, wherein said cycloalkyl, heterocycloalkyl, aryl or heteroaryl groups may be fused with 1-2 further cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, an acyl moiety, unsubstituted or substituted C_1-C_6-alkyl aryl, unsubstituted or substituted C_1-C_6-alkyl heteroaryl, unsubstituted or substituted C_1-C_6-alkenyl aryl, unsubstituted or substituted C_1-C_6-alkenyl heteroaryl, unsubstituted or substituted C_1-C_6-alkynyl aryl, unsubstituted or substituted C_1-C_6-alkynyl heteroaryl, unsubstituted or substituted C_1-C_6-alkyl cycloalkyl, unsubstituted or substituted C_1-C_6-alkyl heterocycloalkyl, unsubstituted or substituted C_1-C_6-alkenyl cycloalkyl, unsubstituted or substituted C_1-C_6-alkenyl heterocycloalkyl, unsubstituted or substituted C_1-C_6-alkynyl cycloalkyl, unsubstituted or substituted C_1-C_6-alkynyl heterocycloalkyl, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted aminocarbonyl, substituted or unsubstituted C_1-C_6-alkyl carboxy, substituted or unsubstituted C_1-C_6-alkyl acyl,

substituted or unsubstituted aryl acyl, substituted or unsubstituted heteroaryl acyl, substituted or unsubstituted C_3-C_8-(hetero)cycloalkyl acyl, unsubstituted or substituted C_1-C_6-alkyl acyloxy, unsubstituted or substituted C_1-C_6-alkyl alkoxy, unsubstituted or substituted C_1-C_6-alkyl alkoxycarbonyl, unsubstituted or substituted C_1-C_6-alkyl aminocarbonyl, unsubstituted or substituted C_1-C_6-alkyl acylamino, acylamino, unsubstituted or substituted C_1-C_6-alkyl ureido, substituted or unsubstituted C_1-C_6-alkyl carbamate, unsubstituted or substituted C_1-C_6-alkyl amino, unsubstituted or substituted C_1-C_6-alkyl ammonium, unsubstituted or substituted C_1-C_6-alkyl sulfonyloxy, unsubstituted or substituted C_1-C_6-alkyl sulfonyl, unsubstituted or substituted C_1-C_6-alkyl sulfinyl, unsubstituted or substituted C_1-C_6-alkyl sulfanyl, unsubstituted or substituted C_1-C_6-alkyl sulfonylamino, unsubstituted or substituted C_1-C_6-alkyl aminosulfonyl, hydroxy, halogen (e.g. chlorine, bromine or fluorine), cyano.

According to a specific embodiment R^2 is an amino group of the formula $-NR^3R^4$ wherein R^3 and R^4 are each independently from each other H, unsubstituted or substituted C_1-C_6-alkyl, unsubstituted or substituted C_2-C_6-alkenyl, unsubstituted or substituted C_2-C_6-alkynyl, unsubstituted or substituted C_1-C_6-alkoxy, unsubstituted or substituted C_1-C_6-sulfanyl, unsubstituted or substituted primary, secondary or tertiary amino groups, aminoacyl, aminocarbonyl, unsubstituted or substituted C_1-C_6 alkoxycarbonyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, carboxy, hydroxy, sulfinyl, sulfonyl, or sulfonamides.

Other specific substituents R^2 are those wherein R^2 is an amino moiety of the formula $-NHR^4$ with R^4 being an unsubstituted straight or branched C_1-C_6 alkyl which may be substituted by unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, amino, alkoxycarbonyl, acylamino, diacylamino.

More specific R^2 are those wherein R^2 is $-NHR^4$ in which R^4 is a straight or branched C_2-C_4 alkyl, in particular an ethylene or propylene moiety, optionally substituted with an

unsubstituted or substituted heteroaryl group, e.g., an unsubstituted or substituted pyridyl or a 2-pyrrolidinone (2-oxopyrrolidine) or a triazolyl moiety.

In a further embodiment R^2 is -NHR^4 in which R^4 is a straight or branched C_2-C_3 alkyl which is substituted by an amine or a cyclic amine like

R^0 is selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C_1-C_6-alkyl, unsubstituted or substituted C_2-C_6-alkenyl, unsubstituted or substituted C_2-C_6-alkynyl, unsubstituted or substituted C_1-C_6-alkyl-aryl, unsubstituted or substituted aryl or unsubstituted or substituted heteroaryl, unsubstituted or substituted C_1-C_6-alkyl-heteroaryl, -C(O)-OR^5, -C(O)-R^5, -C(O)-$NR^5R^{5'}$, -$(SO_2)R^5$, with R^5 and $R^{5'}$ being independently selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6 alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted C_1-C_6-alkyl unsubstituted or substituted aryl, or unsubstituted or substituted C_1-C_6-alkyl heteroaryl wherein said heteroaryl is an unsubstituted or substituted moiety. In a particular embodiment, R^0 is hydrogen.

R^1 is selected from the group comprising or consisting of hydrogen, unsubstituted or substituted C_1-C_6-alkyl, unsubstituted or substituted C_2-C_6-alkenyl, unsubstituted or substituted C_2-C_6-alkynyl, unsubstituted or substituted C_1-C_6-alkoxy, unsubstituted or substituted C_1-C_6-sulfanyl, primary, secondary or tertiary amino groups, aminoacyl, aminocarbonyl, unsubstituted or substituted C_1-C_6 alkoxycarbonyl, unsubstituted or substituted C_3-C_8-cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfinyl, sulfonyl, sulfonamide or hydrazide.

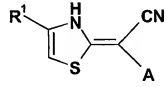
According to a further embodiment, R^1 is selected from unsubstituted or substituted C_3-C_8-cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl

or unsubstituted or substituted heteroaryl group wherein each of the above-mentioned groups may be substituted with at least one moiety selected from the group consisting of C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-sulfanyl, primary, secondary or tertiary amino groups, acylamino, aminocarbonyl, C_1-C_6 alkoxycarbonyl, C_3-C_8-cycloalkyl, C_3-C_8 heterocycloalkyl, aryl, heteroaryl, carboxy, cyano, halogen, hydroxy, nitro, sulfinyl, sulfonyl, sulfonamide or hydrazide.

In a more specific embodiment, R^1 is either a phenyl group which may be substituted by straight or branched C_1-C_6 alkyl or a halogen including fluorine, chlorine. Alternatively, R^1 may be a straight or branched C_1-C_6 alkyl, including methyl, ethyl, propyl isopropyl, t-butyl.

In a more specific embodiment according to the invention, R^1 is unsubstituted or substituted (C_3-C_8)-cycloalkyl, unsubstituted or substituted (C_3-C_8)-heterocycloalkyl, unsubstituted or substituted aryl or unsubstituted or substituted heteroaryl group which may be substituted with at least one moiety selected from the group consisting of unsubstituted or substituted C_1-C_6-alkyl, unsubstituted or substituted C_2-C_6-alkenyl, unsubstituted or substituted C_2-C_6-alkynyl, unsubstituted or substituted C_1-C_6-alkoxy, C_1-C_6-sulfanyl, primary, secondary or tertiary amino groups, aminoacyl, aminocarbonyl, C_1-C_6 alkoxycarbonyl, unsubstituted or substituted C_3-C_8-cycloalkyl, unsubstituted or substituted C_3-C_8 heterocycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfinyl, sulfonyl, sulfonamide or hydrazide, while X is as above defined, A is a pyrimidinyl group which is substituted by halogen or -NHR^4 with R^4 being an unsubstituted or substituted straight or branched C_1-C_6 alkyl in which said alkyl is substituted with unsubstituted or substituted C_3-C_8-cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl or unsubstituted or substituted heteroaryl straight or branched C_1-C_6 alkyl group substituted with an unsubstituted or substituted heteroaryl group and R^0 is hydrogen.

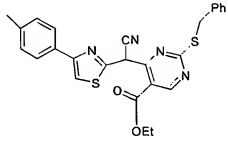
An even more specific embodiment according to the invention relates to compounds of the following formula (I') :

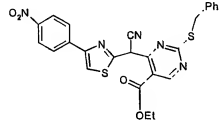


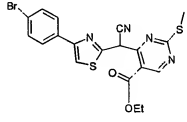
(I')

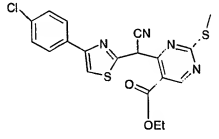
R^1 is an unsubstituted or substituted phenyl or or a straight or branched C_1-C_6 alkyl, or a halogen, A is a pyrimidinyl group which may be substituted with R^2 wherein R^2 is halogen or -NHR^4 in which R^4 is an unsubstituted or substituted straight or branched C_1-C_6 alkyl group which may be substituted with an unsubstituted or substituted pyridyl group.

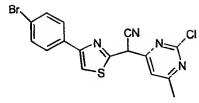
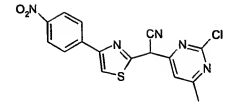
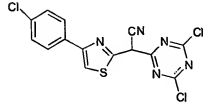
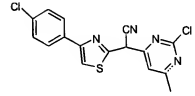
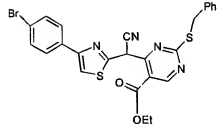
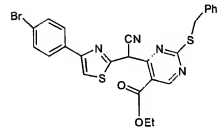
The following compounds appear to be not novel as they are listed in a commercial library ("Explorarory Library", Ambinter, 21.1.2002):









No medical use and no biological activity is disclosed for the above compounds, though.

Specific azole derivatives according to formula (I) are :

(2-chloropyrimidin-4-yl)-(4-ethyl-3H-thiazol-2ylidene)-acetonitrile

[4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-chloropyrimidin-4-yl)acetonitrile

(2-chloropyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(2-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(2-chloropyrimidin-4-yl)[4-(4-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile

ethyl-2-[(2-chloropyrimidin-4-yl)(cyano)methylene]-2,3-dihydro-1,3-thiazole-4-carboxylate

methyl-2-[(2-chloropyrimidin-4-yl)(cyano)methylene]-2,3-dihydro-1,3-thiazole-4-carboxylate

(2-chloropyrimidin-4-yl)[4-(3-methoxyphenyl)-1,3-thiazol-2-yl]acetonitrile

(2-chloropyrimidin-4-yl)[4-(2-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile

(2-chloropyrimidin-4-yl)[4-(4-fluorophenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile

(2-chloro-5-methylpyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile
(2-chloropyrimidin-4-yl)[4-(3,4-dichlorophenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile
(2-chloropyrimidin-4-yl)[4-(4-methylphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile
(4-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-2-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile
4-{2-[(2-chloropyrimidin-4-yl)(cyano)methylene]-2,3-dihydro-1,3-thiazol-4-yl}benzonitrile
[4-(2-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-chloropyrimidin-4-yl)acetonitrile
[4-(3-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-chloropyrimidin-4-yl)acetonitrile
(2-chloropyrimidin-4-yl)[4-(4-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile
(2-chloropyrimidin-4-yl)[4-(pentafluoroethyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile
(2-chloro-5-methylpyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile
(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-chloro-5-methylpyrimidin-4-yl)acetonitrile
(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-chloropyrimidin-4-yl)acetonitrile
(2-chloropyrimidin-4-yl)(4-isopropyl-1,3-thiazol-2(3H)-ylidene)acetonitrile
(2-chloro-5-methylpyrimidin-4-yl)[4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile
(4-chloro-6-morpholin-4-yl-1,3,5-triazin-2-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile
[4-chloro-6-(dimethylamino)-1,3,5-triazin-2-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile
[4-chloro-6-(methylamino)-1,3,5-triazin-2-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile
(2-chloro-6-methylpyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile
(2-chloro-5-methylpyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile
(6-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile
[4-chloro-6-(methylamino)-1,3,5-triazin-2-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile
(2-chloro-6-methylpyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{2-chloro-6-[methyl(phenyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(4-chloro-6-morpholin-4-yl-1,3,5-triazin-2-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(4-ethyl-1,3-thiazol-2(3H)-ylidene)(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

[4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

(4-phenyl-1,3-thiazol-2(3H)-ylidene){2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

{2-[(3-aminopropyl)amino]pyrimidin-4-yl}(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(2-{[2-(6-aminopyridin-3-yl)ethyl]amino}pyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{2-[(3-aminopropyl)amino]pyrimidin-4-yl}(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{2-[(3-aminopropyl)amino]pyrimidin-4-yl}(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

ethyl-2-[cyano(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)methylene]-2,3-dihydro-1,3-thiazole-4-carboxylate

(4-methyl-1,3-thiazol-2(3H)-ylidene){2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

4-(4-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

2-[cyano(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)methylene]-2,3-dihydro-1,3-thiazole-4-carboxylic acid

methyl-2-[cyano(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)methylene]-2,3-dihydro-1,3-thiazole-4-carboxylate

methyl-2-(cyano{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}methylene)-2,3-dihydro-1,3-thiazole-4-carboxylate

[2-(cyclopropylamino)pyrimidin-4-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

4-[2-({4-[cyano(4-methyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)ethyl]benzenesulfonamide

[4-(pentafluoroethyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

[2-(cyclopropylamino)pyrimidin-4-yl][4-(pentafluoroethyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile

(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(4-ethyl-1,3-thiazol-2(3H)-ylidene){2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

[4-(3-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

[4-(3-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene](2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

methyl 4-[2-({4-[cyano(4-ethyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)ethyl]benzoate

6-{[2-({4-[-cyano(4-ethyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)ethyl]amino}nicotinonitrile

[2-({2-[6-(dimethylamino)pyridin-3-yl]ethyl}amino)pyrimidin-4-yl](4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

4-[2-({4-[cyano(4-ethyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)ethyl]benzenesulfonamide

(2-{[2-(4-aminophenyl)ethyl]amino}pyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(4-ethyl-1,3-thiazol-2(3H)-ylidene)(2-{[2-(6-morpholin-4-ylpyridin-3-yl)ethyl]amino}pyrimidin-4-yl)acetonitrile

(4-ethyl-1,3-thiazol-2(3H)-ylidene)[2-({2-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]ethyl}amino)pyrimidin-4-yl]acetonitrile

[2-(cyclopropylamino)pyrimidin-4-yl](4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[4-(2-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

[4-(2-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene](2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

[4-(4-fluorophenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

[4-(4-fluorophenyl)-1,3-thiazol-2(3H)-ylidene](2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

(4-ethyl-1,3-thiazol-2(3H)-ylidene){5-methyl-2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

(4-ethyl-1,3-thiazol-2(3H)-ylidene)(5-methyl-2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

[2-(cyclopropylamino)-5-methylpyrimidin-4-yl](4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(4-ethyl-1,3-thiazol-2(3H)-ylidene){2-[(3-pyrrolidin-1-ylpropyl)amino]pyrimidin-4-yl}acetonitrile

[2-({2-[(5-nitropyridin-2-yl)amino]ethyl}amino)pyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

6-{[2-({4-[cyano(4-phenyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)ethyl]amino}nicotinonitrile

tert-butyl 4-({4-[cyano(4-phenyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)butanoate

[4-(4-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene](2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

(4-methyl-1,3-thiazol-2(3H)-ylidene)(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

(4-tert-butyl-1,3-thiazol-2(3H)-ylidene){2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)[2-(cyclohexylamino)pyrimidin-4-yl]acetonitrile

(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)[2-(cyclopropylamino)pyrimidin-4-yl]acetonitrile

[4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

[4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene][2-(cyclopropylamino)pyrimidin-4-yl]acetonitrile

[4-(3,4-dichlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

[4-(3,4-dichlorophenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

[2-(cyclopropylamino)pyrimidin-4-yl][4-(3,4-dichlorophenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile

[4-(4-methylphenyl)-1,3-thiazol-2(3H)-ylidene](2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

[4-(4-methylphenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

[2-(cyclopropylamino)pyrimidin-4-yl][4-(4-methylphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile

{2-[(3-aminopropyl)amino]pyrimidin-4-yl}(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{2-[(2-aminoethyl)amino]pyrimidin-4-yl}(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{2-[(piperidin-4-yl)amino]pyrimidin-4-yl}(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

methyl N-{4-[(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(cyano)methyl]pyrimidin-2-yl}-beta-alaninate

(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)[4-(pentafluoroethyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile

{5-methyl-2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(5-methyl-2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[2-(cyclopropylamino)-5-methylpyrimidin-4-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(4-tert-butyl-1,3-thiazol-2(3H)-ylidene){5-methyl-2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(5-methyl-2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)[2-(cyclopropylamino)-5-methylpyrimidin-4-yl]acetonitrile

(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(5-methyl-2-{[3-(1H-1,2,4-triazol-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

N-[3-({4-[(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(cyano)methyl]pyrimidin-2-yl}amino)propyl]-2-ethoxy-N-glycoloylacetamide

N-[3-({4-[cyano(4-isopropyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)propyl]-2-ethoxy-N-glycoloylacetamide

[2-(cyclohexylamino)pyrimidin-4-yl](4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[2-(cyclopentylamino)pyrimidin-4-yl](4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(4-ethyl-1,3-thiazol-2(3H)-ylidene)[2-(isobutylamino)pyrimidin-4-yl]acetonitrile

(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-{[3-(1H-1,2,4-triazol-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

(4-isopropyl-1,3-thiazol-2(3H)-ylidene)(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

(4-isopropyl-1,3-thiazol-2(3H)-ylidene){2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

[2-(cyclopropylamino)pyrimidin-4-yl](4-isopropyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

methyl 4-({4-[(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(cyano)methyl]pyrimidin-2-yl}amino)butanoate

4-{2-[cyano(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)methylene]-2,3-dihydro-1,3-thiazol-4-yl}benzonitrile

4-[2-(cyano{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}methylene)-2,3-dihydro-1,3-thiazol-4-yl]benzonitrile

4-(2-{cyano[2-(cyclopropylamino)pyrimidin-4-yl]methylene}-2,3-dihydro-1,3-thiazol-4-yl)benzonitrile

[4-(2-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

[4-(3-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

[4-(3-chlorophenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

[4-(2-chlorophenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

[2-(cyclopropylamino)pyrimidin-4-yl][4-(4-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile

[4-(2-chlorophenyl)-1,3-thiazol-2(3H)-ylidene][2-(cyclopropylamino)pyrimidin-4-yl]acetonitrile

N-[3-({4-[cyano(4-ethyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)propyl]acetamide

N-[2-({4-[(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(cyano)methyl]pyrimidin-2-yl}amino)ethyl]acetamide

{2-[(1-acetylpiperidin-4-yl)amino]pyrimidin-4-yl}(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-{[3-(2,5-dioxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

(2-{[3-(2,5-dioxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(4-ethyl-1,3-thiazol-2(3H)-ylidene)(2-{[1-(methylsulfonyl)piperidin-4-yl]amino}pyrimidin-4-yl)acetonitrile trifluoroacetate

N~3~-{4-[(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(cyano)methyl]pyrimidin-2-yl}-N~1~,N~1~-dimethyl-beta-alaninamide

N-{3-[{4-[(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(cyano)methyl]pyrimidin-2-yl}(methyl)amino]propyl}acetamide

N-[3-({4-[(4-tert-butyl-3-methyl-1,3-thiazol-2(3H)-ylidene)(cyano)methyl]pyrimidin-2-yl}amino)propyl]acetamide

(4-ethyl-1,3-thiazol-2(3H)-ylidene)(2-{[4-(morpholin-4-ylmethyl)benzyl]oxy}pyrimidin-4-yl)acetonitrile

{2-[3-(dimethylamino)propoxy]pyrimidin-4-yl}(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene]{5-methyl-2-[(3-pyrrolidin-1-ylpropyl)amino]pyrimidin-4-yl}acetonitrile

[4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(3-pyrrolidin-1-ylpropyl)amino]pyrimidin-4-yl}acetonitrile

[4-(dimethylamino)-6-(octahydroquinolin-1(2H)-yl)-1,3,5-triazin-2-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[2-(cyclohexylamino)-5-methylpyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[2-(cyclohexylamino)pyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[4-(methylamino)-6-(4-methylpiperidin-1-yl)-1,3,5-triazin-2-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[4-(cyclohexylamino)-6-(methylamino)-1,3,5-triazin-2-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[5-methyl-2-(4-methylpiperidin-1-yl)pyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[2-(cyclopropylamino)-5-methylpyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[2-(cyclopropylamino)pyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[2-(cyclopentylamino)-5-methylpyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{5-methyl-2-[(1-methylbutyl)amino]pyrimidin-4-yl}(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[2-(cyclopentylamino)pyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{5-methyl-2-[(3-pyrrolidin-1-ylpropyl)amino]pyrimidin-4-yl}(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{2-[(1-methylbutyl)amino]pyrimidin-4-yl}(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{6-[(2-furylmethyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[6-(4-ethylpiperazin-1-yl)pyrimidin-4-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(4-phenyl-1,3-thiazol-2(3H)-ylidene){2-[(3-pyrrolidin-1-ylpropyl)amino]pyrimidin-4-yl}acetonitrile

[2-(cyclopentylamino)-6-methylpyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[4-(4-ethylpiperazin-1-yl)-6-morpholin-4-yl-1,3,5-triazin-2-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{2-[(cyclohexylmethyl)amino]pyrimidin-4-yl}(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{2-[(cyclohexylmethyl)amino]-5-methylpyrimidin-4-yl}(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[2-(4-ethylpiperazin-1-yl)-5-methylpyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[4-(cyclopentylamino)-6-(methylamino)-1,3,5-triazin-2-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[4-(cyclopropylamino)-6-morpholin-4-yl-1,3,5-triazin-2-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[4-(cyclopropylamino)-6-(methylamino)-1,3,5-triazin-2-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[4-(cyclopropylamino)-6-(methylamino)-1,3,5-triazin-2-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[2-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-5-methylpyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(5-methyl-2-{[3-(1H-1,2,4-triazol-1-yl)propyl]amino}pyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{2-[(1,4-dimethylpentyl)amino]-5-methylpyrimidin-4-yl}(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(5-methyl-2-{[2-(1H-pyrazol-1-yl)ethyl]amino}pyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(4-phenyl-1,3-thiazol-2(3H)-ylidene)(2-{[3-(1H-1,2,4-triazol-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

(4-phenyl-1,3-thiazol-2(3H)-ylidene)(2-{[2-(1H-pyrazol-1-yl)ethyl]amino}pyrimidin-4-yl)acetonitrile

[2-(dipropylamino)-5-methylpyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{2-[(1,4-dimethylpentyl)amino]pyrimidin-4-yl}(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[2-(methylamino)pyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[4-[(1,4-dimethylpentyl)amino]-6-(methylamino)-1,3,5-triazin-2-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[4-{[(6-aminopyridin-3-yl)methyl]amino}-6-(methylamino)-1,3,5-triazin-2-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[2-(methylamino)pyrimidin-4-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[2-(cyclopentylamino)pyrimidin-4-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[2-(cyclohexylamino)pyrimidin-4-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{2-[(1-methylbutyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[2-(cyclopentylamino)-6-methylpyrimidin-4-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{2-[(cyclohexylmethyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{6-[methyl(phenyl)amino]-2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{2-[(2,3-dimethylcyclohexyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(4-methyl-1,3-thiazol-2(3H)-ylidene){2-[(pyridin-3-ylmethyl)amino]pyrimidin-4-yl}acetonitrile

{6-methyl-2-[(2-pyridin-2-ylethyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[2-(isopropylamino)pyrimidin-4-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{2-[(1,2-dimethylpropyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(4-methyl-1,3-thiazol-2(3H)-ylidene){2-[4-(pyrimidin-2-ylamino)piperidin-1-yl]pyrimidin-4-yl}acetonitrile

{2-[(1-ethylpropyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{2-[(3-butoxypropyl)amino]-6-[methyl(phenyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{4-[(3-butoxypropyl)amino]-6-morpholin-4-yl-1,3,5-triazin-2-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{2-(isopropylamino)-6-[methyl(phenyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

{2-[(3-isopropoxypropyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

[4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene][2-(cyclopropylamino)pyrimidin-4-yl]acetonitrile

[4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene][2-(cyclopentylamino)pyrimidin-4-yl]acetonitrile
[4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(cyclohexylmethyl)amino]-5-methylpyrimidin-4-yl}acetonitrile

Compounds of formula (I) are suitable for the use as medicament, in particular for the treatment and/or prevention of neurodegenerative diseases, neuronal disorders including epilepsy, Alzheimer's disease, amyotrohic lateral sclerosis, parkinsonism-dementia of Gaum, corticobasal degeneration, dementia pugilistica and head trauma, Down's syndrome, postencephalatic parkinsoism, progressive supranuclear palsy, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's Disease, HIV dementia, ischemic stroke and head trauma retinal diseases, spinal cord injury, head trauma, mood disorders, particularly bipolar (mood) disorders, multiple sclerosis or amyotrophic lateral sclerosis, diabetes, particularly type II diabetes and obesity, asthma, septic shock, transplant rejection, cerebrovascular accident, glaucoma, cardiovascular diseases including stroke, arteriosclerosis, myocardial infarction, myocardial reperfusion injury, ischemia, cancer and inflammatory diseases including arteriosclerosis, arthritis, Inflammatory Bowel Disease or rheumatoid arthritis.

A further aspect of the present invention is related to the use of the azole derivatives according to formula (I) for the preparation of pharmaceutical compositions for the modulation - notably of the inhibition - of a protein kinase mediated signalling pathways as well as for preventive and therapeutic treatment of diseases caused by abnormal protein kinase activity. Preferably, this protein kinase is a c-Jun Kinase. More preferably said protein is a Glycogen Synthase Kinase 3, particularly Glycogen Synthase Kinase 3 beta. The compounds according to formula I could be employed alone or in combination with further pharmaceutical agents.

Specifically, the compounds pursuant to formula (I) are useful in the preparation of a medicament for the prevention and/or treatment of pathological states and diseases in

which inhibition of protein kinases, particularly of Jun Kinase and/or Glycogen Synthase Kinase 3 is required. These diseases are selected in the group consisting of neurodegenerative diseases, neuronal disorders including epilepsy, Alzheimer's disease, Parkinson's disease, retinal diseases, spinal cord injury, head trauma, multiple sclerosis or amyotrophic lateral sclerosis, diabetes, particularly type II diabetes and obesity, asthma, septic shock, transplant rejection, cerebrovascular accident, glaucoma, cardiovascular diseases including stroke, arteriosclerosis, myocardial infarction, myocardial reperfusion injury, ischemia, cancer and inflammatory diseases including arteriosclerosis, arthritis, Inflammatory Bowel Disease or rheumatoid arthritis.

Specifically, the compounds of formula I are suitable for use in treating disorders of the immune system and neuronal system of mammals, notably of human beings. Such neuronal system disorders include for example neurodegenerative diseases e.g. Alzheimer's disease, Huntington's disease, Parkinson's disease, retinal diseases, spinal cord injury, multiple sclerosis or amyotrophic lateral sclerosis, head trauma, epilepsy and seizures, ischemic and hemorragic brain strokes.

Also, the compounds of formula I are suitable for use in the treatment and/or prevention of metabolic disorders mediated by insulin resistance or hyperglycemia, comprising diabetes type I and/or II, inadequate glucose tolerance, insulin resistance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, obesity, polycystic ovary syndrome (PCOS).

Immune system disorders include for example asthma, transplant rejection, inflammatory processes such as inflammatory bowel disease (IBD), cartilage and bone erosion disorders, rheumatoid arthritis, septic shock.

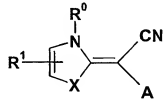
The compounds according to formula I are also suitable for use in treating cancers, such as breast, colorectal, pancreatic, prostate, testicular, ovarian, lung, liver and kidney cancers.

In another embodiment, the compounds according to formula I may be used for treating cardiovascular diseases including atherosclerosis, restenosis, glaucoma, stroke, ischemia, e.g. cerebral ischemia, myocardial reperfusion injury or myocardial infarction.

In another embodiment, the compounds according to formula I may be used for treating various ischemic conditions including heart and kidney failures, hepatic disorders and brain reperfusion injuries.

Another object of the present invention is a method for the treatment of disease states mediated by protein kinase comprising the administration to the patient of a pharmaceutically active amount of an azole derivative according to formula (I).

Still a further object of the present invention is a process for preparing the novel azole derivatives according to formula I.



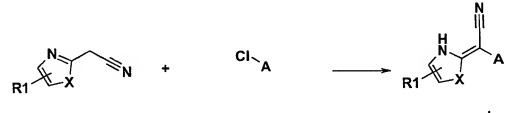
(I)

The azole methylidene cyanide exemplified in this invention may be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred experimental conditions (i.e., reaction temperatures, time, moles of reagents, solvents, etc.) are given, other experimental conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by one skilled in the art by routine optimisation procedures.

Generally, azole methylidene cyanide derivatives according to the general formula I may be obtained by several processes using solution-phase chemistry protocols.

According to one process, azole methylidene cyanide derivatives according to the general formula I, whereby the substituents X, A and R^1 are as above defined and R^0 is H, are prepared from the corresponding acetonitrile derivatives II and chloro derivatives III, by well known solution-phase chemistry protocols, such as those described in the Examples and shown in Scheme 1, below.

Scheme 1

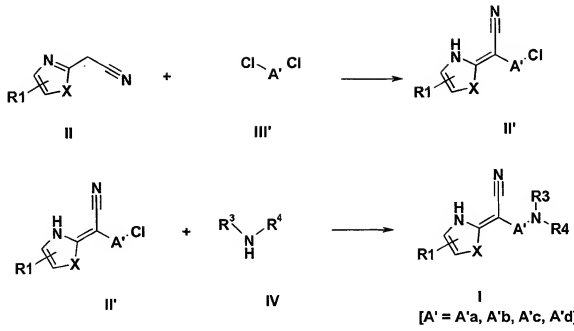


II III I

The chloro derivatives III can be obtained either through commercial sources or can be prepared from known compounds by conventional procedures known by one skilled in the art. Preferred chloro derivatives III are defined such as shown in the scheme 2 below.

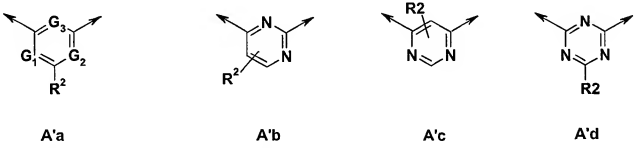
The azole methylidene cyanide of general formula I are prepared according to a general process outlined above, and also starting from the azole acetonitrile derivatives II, whereby X and R^1 are as above defined and R^0 is hydrogen, which was reacted with the bis-chloro derivatives III', where A' is as above defined, to give the intermediate of synthesis II'. In a subsequent step, the intermediate II' was treated with the amines IV, whereby the substituents R^3,R^4 are as above defined to give the final azole methylidene cyanide derivatives I, utilizing well known solution-phase chemistry protocols, such as those described in the Examples and shown in Scheme 2, below

Scheme 2



and whereby A' is either a pyrimidinyl or triazinyl core A'a, A'b, A'c, A'd as shown in the Scheme 3 below, and whereby R^2 is as above defined and also G^1, G^2 and G^3 are independently from each other selected from N and CH.

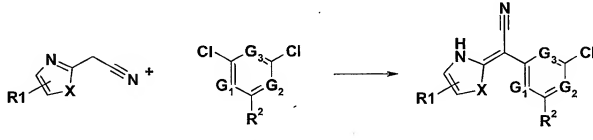
Scheme 3

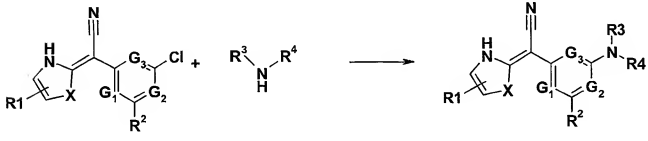


The azole methylidene cyanide derivatives according to the general formula Ia, whereby the substituent X and R1 are as above defined and R^0 is hydrogen, were obtained in two subsequent steps as shown in Scheme 4. In a first step, the chloro azole methylidene cyanide derivatives II'a were isolated after condensation of the azole acetonitrile compound II with a bis-chloro derivative III'a, whereby the heteroaromatic core is A'a, and R^2 is as above defined and also G^1, G^2 and G^3 are independently from each other selected from N and CH. This first reaction step was performed using, e.g. lithium hydride or sodium hydride or similar reagents in an appropriate solvent such as THF or DMF in an anhydrous

inert atmosphere. This reaction can be performed at various temperatures (range of about – 78°C to 160° C, *Pol. J. Chem.* by Chabaka L.M. et al. p.1317-1326 (1994)) or reaction times depending of the intrinsic reactivity of compounds II and III'a, by traditional thermic method or using microwave technology, using standard conditions well known to the person skilled in the art, such as those described hereinafter in the Examples. In a subsequent step, the chloro azole methylidene cyanide derivatives II'a were treated with various amines IV to give the expected azole methylidene cyanide Ia. The nucleophilic displacement of the chloro atom of the heterocyclic moiety by the amine IV, is accomplished by treatment with several equivalents of the amines IV in presence or absence of sodium iodine as catalyst and a base such as triethylamine or diisopropyl-ethylamine or similar reagents. This reaction can be performed at various temperatures depending of the intrinsic reactivity of compounds IV and II'a, by traditional thermic method or using microwave technology, using standard conditions well known to the person skilled in the art, such as those described hereinafter in the Examples.

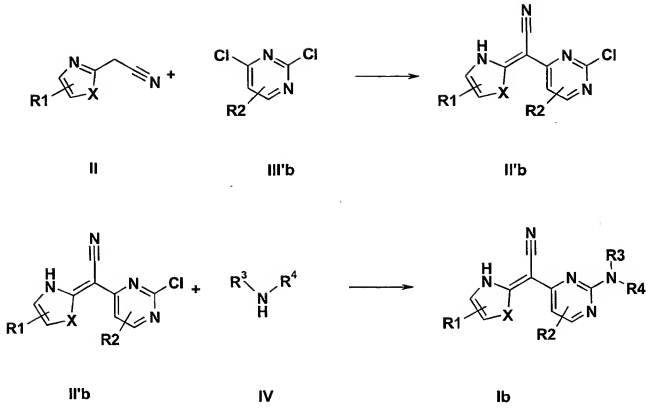
Scheme 4





The azole methylidene cyanide derivatives according to the general formula Ib, whereby the substituent X and R^1 are as above defined and R^0 is hydrogen, were obtained in two subsequent steps as shown in Scheme 5. In a first step, the chloro azole methylidene cyanide derivatives II'b were isolated after condensation of the azole acetonitrile compound II with bis-chloro derivative III'b, whereby the heteroaromatic core is A'b, and R^2 is as above defined. This first reaction step was performed, using, e.g. lithium hydride or sodium hydride or similar reagents in an appropriate solvent such as THF or DMF. This reaction can be performed at various temperature depending of the intrinsic reactivity of compounds II and III'b, by traditional thermic method or using microwave technology, using standard conditions well known to the person skilled in the art, such as those described hereinafter in the Examples. In a subsequent step, chloro azole methylidene cyanide derivatives II'b were treated with various amines IV to give the azole methylidene cyanide derivatives Ib. The nucleophilic displacement of the chloro atom of the pyrimidinyl moiety by the amine IV, is accomplished by treatment with several equivalents of the amines IV in presence or absence of sodium iodine as catalyst and a base such as triethylamine or diisopropylethylamine or similar reagents. This reaction can be performed at various temperatures depending of the intrinsic reactivity of compounds IV and II'b, by traditional thermic method or using microwave technology, using standard conditions well known to the person skilled in the art, such as those described hereinafter in the Examples.

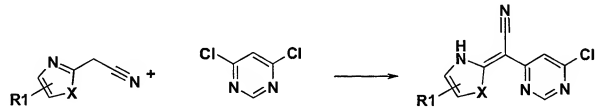
Scheme 5



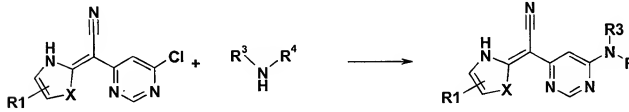
The azole methylidene cyanide derivatives according to the general formula Ic, whereby the substituent X and R1 are as above defined and R^0 is hydrogen, were obtained in two subsequent steps as shown in Scheme 6. In a first step, the azole methylidene cyanide derivatives II'c were isolated after condensation of the azole acetonitrile compound II with a bis-chloro derivative III'c, whereby the heteroaromatic core is A'c, and R^2 is as above defined. This first reaction step was performed, using, e.g. lithium hydride or sodium hydride or similar reagents in an appropriate solvent such as THF or DMF. This reaction can be performed at various temperatures depending of the intrinsic reactivity of compounds II and III'c, by traditional thermic method or using microwave technology, using standard conditions well known to the person skilled in the art, such as those described hereinafter in the Examples. In a subsequent step, the chloro azole methylidene cyanide derivatives II'c were treated with various amines IV to give the expected azole methylidene cyanide acetonitriles derivatives Ic. The nucleophilic displacement of the chloro atom of the pyrimidinyl moiety by the amine IV, is accomplished by treatment with

several equivalents of the amines IV in presence or absence of sodium iodine as catalyst and a base such as triethylamine or diisopropylethylamine or similar reagents. This reaction can be performed at various temperatures depending of the intrinsic reactivity of compounds IV and II'c, by traditional thermic method or using microwave technology, using standard conditions well known to the person skilled in the art, such as those described hereinafter in the Examples.

Scheme 6



II III'c II'c

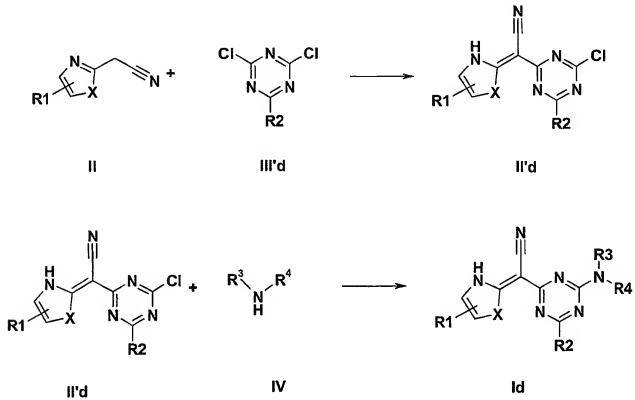


II'c IV Ic

The azole methylidene cyanide derivatives according to the general formula Id, whereby the substituent X and R^1 is as above defined and R^0 is hydrogen, were obtained in two subsequent steps as shown in Scheme 7. In a first step, the azole methylidene cyanide derivatives II'd were isolated after condensation of the azole acetonitrile compound II with a bis-chloro derivative III'd, whereby the heteroaromatic core is A'd, and R^2 is as above defined. This first reaction step was performed, using, e.g. lithium hydride or sodium hydride or similar reagents in an appropriate solvent such as THF or DMF. This reaction can be performed at various temperature depending of the intrinsic reactivity of compounds

II and III'd, by traditional thermic method or using microwave technology, using standard conditions well known to the person skilled in the art, such as those described hereinafter in the Examples. In a subsequent step, the chloro azole methylidene cyanide derivatives II'd were treated with various amines IV to give the expected azole methylidene cyanide derivatives Id. The nucleophilic displacement of the chloro atom of the triazinyl moiety by the amine IV, is accomplished by treatment with several equivalents of the amines IV in presence or absence of sodium iodine as catalyst and a base such as triethylamine or diisopropylethylamine or similar reagents. This reaction can be performed at various temperature depending of the intrinsic reactivity of compounds IV and II'd, by traditional thermic method or using microwave technology, using standard conditions well known to the person skilled in the art, such as those described hereinafter in the Examples.

Scheme 7

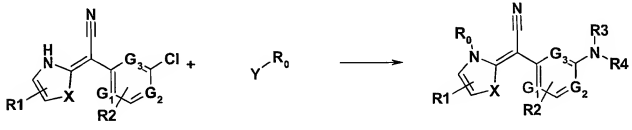


The azole methylidene cyanide derivatives according to the general formula Ie, whereby the substituent X, R^0 and R^1 is as above defined, were obtained in one step as shown in Scheme 8, by the treatment of the azole methylidene cyanide derivatives II'a with

electrophiles Y-R^0 such as alkyl, benzyl halides or acyl chlorides at a temperature in the range of 25°C to 80°C in the presence of a base such as potassium carbonate, potassium ter-butoxide, sodium hydride and the like in a solvent such as DMSO, DMF, acetone and the like in an anhydrous inert atmosphere.

Electrophiles Y-R^0 are either commercially available or can be prepared from known compounds by conventional procedures known by one skilled in the art. Preferred electrophiles as starting materials include methyl iodide and acetyl chloride.

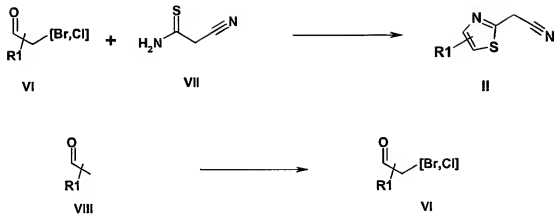
Scheme 8



II'a V Ie

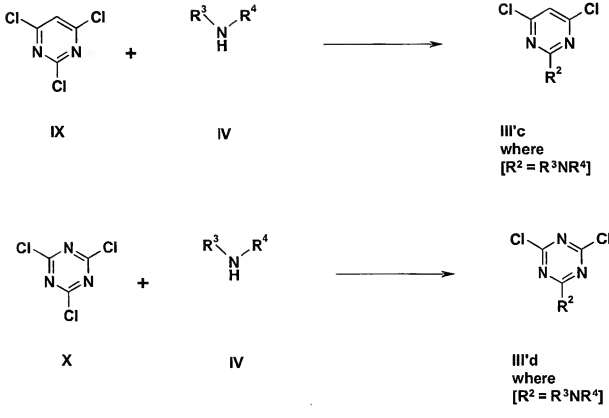
The azole acetonitrile components II are either obtained from commercial sources or prepared in one step by conventional procedures from the condensation of the corresponding α-bromo or chloro ketones VI and thioamide derivatives VII as outlined in scheme 9 (*J. Chem. Research* **(S)** by Abdelhamid, A. O. et al, , 144-145 (1995); EP0169502 A2, *J. Chem. Soc. Perkin Trans I* by Brown M.D. et al **52(5)** p.1623-1626 (1985); *J. Chem. Research* by Dawood K. M. et al **(S)**, 206-201 (2000)). The α-bromo ketones VI are either obtained from commercial sources or prepared in one step by conventional procedures known by one skilled in the art by bromination of the corresponding acetone derivatives VIII (Ref: Gaudry M. and Marquet A., Tetrahedron, 1970, 26, 5611-5615)

Scheme 9



The dichloro heterocycles III'a and dichloropyrimidyl components III'b are obtained from commercial sources. The chloropyrimidinyl derivatives III'c are obtained from commercial sources or made from the dichloro pyrimidinyl derivatives IX by treatment of the latter with primary or secondary amines IV, using standard conditions well known to the practitioner skilled in the art, to yield products of formula III'c, as shown in scheme 11. The dichlorotriazinyl derivatives III'd are obtained from commercial sources or made from cyanuric chloride X, by treatment of the latter with primary or secondary amines IV, using standard conditions well known to the practitioner skilled in the art, to yield products of formula III'd, as shown in scheme 11.

Scheme 11



If the above set out general synthetic methods are not applicable for the obtention of compounds of formula I, suitable methods of preparation known by a person skilled in the art should be used.

When employed as pharmaceuticals, the azole derivatives of the present invention are typically administered in the form of a pharmaceutical composition. Hence, pharmaceutical compositions comprising a compound of formula I and a pharmaceutically acceptable carrier, diluent or excipient therefore are also within the scope of the present invention. A person skilled in the art is aware of a whole variety of such carrier, diluent or excipient compounds suitable to formulate a pharmaceutical composition. Also, the present invention provides compounds for use as a medicament. In particular, the invention provides the compounds of formula I for use as protein kinase inhibitor, particularly c-Jun N-terminal Kinase inhibitor and particularly Glycogen Synthase Kinase 3 inhibitor, for the treatment of

disorders and/or diseases as above-mentioned in mammals, notably of humans, either alone or in combination with other medicaments.

The compounds of the invention, together with a conventionally employed adjuvant, carrier, diluent or excipient may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, or in the form of sterile injectable solutions for parenteral (including subcutaneous use). Such pharmaceutical compositions and unit dosage forms thereof may comprise ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

When employed as pharmaceuticals, azole derivatives of this invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Generally, the compounds of this invention are administered in a pharmaceutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

The pharmaceutical compositions of these inventions can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, intrathecal, intraperitoneal and intranasal. Depending on the intended route of delivery, the compounds are preferably formulated as either injectable, topical or oral compositions. The compositions for oral administration may take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit

dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampoules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the azole compound is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatine; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As above mentioned, the benzazole derivatives of formula I in such compositions is typically a minor component, frequently ranging between 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

The above described components for orally administered or injectable compositions are merely representative. Further materials as well as processing techniques and the like are set out in Part 5 of *Remington's Pharmaceutical Sciences*, 20th Edition, 2000, Marck Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

The compounds of this invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can also be found in the incorporated materials in *Remington's Pharmaceutical Sciences*.

In the following the present invention shall be illustrated by means of some examples which are not construed to be viewed as limiting the scope of the invention.

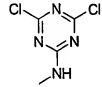
The following abbreviations are hereinafter used in the accompanying examples: min (minute), hr (hour), g (gram), mmol (millimole), m.p. (melting point), eq (equivalents), mL (milliliter), µL (microliters), mL (milliliters), L (Liters), Acetone-d6 (deuteriated actenone), ACN (Acetonitrile), Boc (butoxycarbonyl), Br2 (Bromine), $CDCl_3$ (deuteriated chloroform), $CHCl_3$ (Chloroform), $CsCO_3$ (Cesium carbonate), cHex (Cyclohexanes), CCl_4 (carbon tetrachloride) DCM (Dichloromethane), DIPEA (Diisopropylethylamine), DMA (Dimethylacetamide), DMAP (4- Dimethylaminopyridine) DMF (Dimethylformamide), DMSO (Dimethylsulfoxide), DMSO-d_6 (deuterated dimethylsulfoxide), Et_3N (Triethylamine), EtOAc (Ethyl acetate), EtOH (Ethanol), Et_2O (Diethyl ether), HBr (Hydrobromic acid), HCl (Hydrochloric acid), iPrOH (Isopropanol), K_2CO_3 (potassium carbonate), LAH (lithium aluminium hydride), LiH (Lithium Hydride), MeOH (Methanol), MeOD (deuteriated methanol), NaI (Sodium Iodine), NaH (Sodium hydride), $NaHCO_3$ (Sodium bicarbonate), NaOD (deuteriated sodium hydride), NaOH (sodium hydride), Na_2SO_4 (Sodium sulphate), NH_4Cl (Ammonium chloride), NBS (N- bromo succinimide), NMM (N-methylmorpholine), pet ether (Petrol ether), TEA (Triethyl amine), TFA (Trifluoro-acetic acid), THF (Tetrahydrofuran), TMA (Trimethylaluminium), $MgSO_4$ (Magnesium sulfate), r.t. (room temperature), Rt (Retention time).
The HPLC, NMR and MS data provided in the examples described below were obtained as followed: HPLC: column Waters Symmetry C8 50 x 4.6 mm, Conditions: MeCN/H_2O, 5 to 100% (8 min), max plot 230-400 nm; Mass spectra: PE-SCIEX API 150 EX (APCI and ESI), LC/MS spectra: Waters ZMD (ES); ^{1}H-NMR: Bruker DPX-300MHz.

The purifications were obtained as followed: Preparative HPLC Waters Prep LC 4000 System equipped with columns Prep Nova-Pak®HR C186 µm 60Å, 40x30mm (up to 100mg) or 40x300 mm (up to 1g). All the purifications were performed with a gradient of MeCN/H_2O 0.09% TFA.

Examples

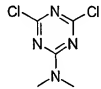
Procedure A

Intermediate 1: 4,6-dichloro-N-methyl-1,3,5-triazin-2-amine



Cyanuric chloride (10 g, 54.3 mmol, 1 equiv.) was dissolved in THF (200 mL) and cooled to -70 °C. DIPEA (36.3 mL, 1.42 mmol, 2 equiv.) and methylamine hydrochloride (3.7g, 1 equiv.) were added to the reaction mixture, which was stirred 2h at -70 °C and 1h at rt. The THF was removed under reduced pressure and the remaining material was taken up in DCM and washed with water. The organic layer was dried with $MgSO_4$ and the DCM removed to give a colourless powder (9.5g, 97%).
MS(ESI^+): 181.2; MS(ESI^-): 179.2.

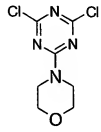
Intermediate 2: 4,6-dichloro-N-dimethyl-1,3,5-triazin-2-amine



Following the general strategies and protocols outlined in the procedure A, the title compound was obtained from cyanuric chloride and dimethylamine in the presence of K_2CO_3 for 2 h at -70°C and 1 h at rt in THF (86%).

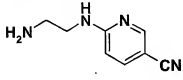
MS(ESI$^+$): 194.3; MS(ESI$^-$): 192.3.

Intermediate 3: 4,6-dichloro-N-morpholinyl-1,3,5-triazin-2-amine



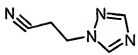
Following the general strategies and protocols outlined in the procedure A, the title compound was obtained from cyanuric chloride and morpholine in the presence of DIPEA for 2 h at -70°C and 1 h at rt in THF (98%).
MS(ESI$^+$):236.1; MS(ESI$^-$): 234.1.

Intermediate 4 : 6-[(2-Aminoethyl)amino]nicotinonitrile



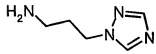
To 100 mL of ethylene diamine at 50°C under nitrogen was added 2-chloro-5-cyanopyridine (10g, 0.0722mol) in small portions over a period of 3h. The reaction mixture was stirred at 50°C for an additional 5h. The reaction mixture was concentrated to near dryness under reduced pressure and the crude residue obtained was purified by chromatography using chloroform/methanol (9/1) as eluent to afford 9g of the title compound as a solid (77%).
^{1}H NMR (DMSO-*d6*) δ 8.37 (d, *J*=2.2Hz, 1H), 7.66-7.58 (m, 2H), 6.54 (d, *J*=9.0Hz, 1H), 3.28-3.16 (m, 2H), 2.68 (t, *J*=6.4Hz, 2H), 1.78-1.40 (br s, 2H).
M$^-$(ES): 161.4.

Intermediate 5 : 3-(1*H*-1,2,4-triazol-1-yl)propan-1-amine
Step-1: 3-(1*H*-1,2,4-triazol-1-yl)propanenitrile



A mixture of 1,2,4-triazole (25g, 0.362mol) and acrylonitrile (100mL, 4w/v) was heated up to 80°C under nitrogen for 16h. The reaction mixture was then concentrated under reduced pressure to remove the excess of acrylonitrile affording 41g of the title compound as a colourless liquid (93%). It was used in the next step without further purification.

Step-2: 3-(1*H*-1,2,4-triazol-1-yl)propan-1-amine

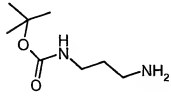


To a mixture of 3-(1*H*-1, 2, 4-triazol-1-yl)-propanenitrile (25g, 0.204mol) and Raney-Nickel (5g, 0.2w/w, wet) in methanol (300mL) was added a solution of 25% aqueous NH_4OH (75mL). The above reaction mixture was hydrogenated under pressure (75 psi of hydrogen) for a period of 6h. The catalyst was then filtered off and the filtrate was concentrated under reduced pressure. The residue obtained was taken up in DCM (150mL) then triturated 4 times and the combined organic layer was concentrated under reduced pressure to yield 22g of the title compound as a liquid (85%). The above compound was converted to its hydrochloride using HCl gas in a mixture of ether/methanol (9.5/0.5) to yield 20g of the product as its dihydrochloride.

^{1}H NMR (DMSO-d_6) δ 8.89 (s, 1H), 8.26 (s, 1H), 7.83 (s, 2H exchangeable), 4.33 (t, J= 6.8Hz, 2H), 2.85-2.74 (m, 2H), 2.13-2.03 (m, 2H).

Intermediate 6: 4-(3-Aminopropyl)morpholine-3,5-dione.HCl

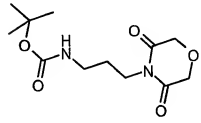
Step1: *Tert*-Butyl-3-aminopropyl carbamate



To a stirred solution of 1,3-diaminopropane (100g, 1.34mol) in dry THF (1L) at 0°C was added Boc-anhydride (98g, 0.45mol) and the resulting solution was stirred at rt for 24h

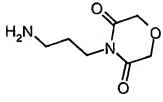
under N_2. The reaction mixture was concentrated under reduced pressure and the crude residue obtained was dissolved in EtOAc (2L). The organic layer was washed with brine (3x250mL), dried with $MgSO_4$ and concentrated to near dryness. The crude product was purified by column chromatography over silica gel (chloroform/methanol and methanol) to give 65g of *tert*-butyl-3-aminopropyl carbamate (82%).

Step 2 : *Tert*-Butyl-3-(3,5-dioxomorpholin-4-yl)propylcarbamate



A mixture of diglycolic anhydride (22g, 0.188mol), *tert*-butyl-3-aminopropylcarbamate (65g, 0.377mol) and NMM (21mL, 0.188mol) in DMA (300mL) was heated up to 120°C for 48h. The reaction mixture was cooled down to r.t and diluted with EtOAc (1.5L). The solution was washed with brine (5x150mL), dried with $MgSO_4$ and concentrated under reduced pressure. The crude was purified by column chromatography over silica gel (15% ethylacetate in chloroform) affording 15g of the title compound (30%).

Step 3 : 4-(3-Aminopropyl)morpholine-3,5-dione hydrochloric salt.



To a solution of *tert*-butyl-3-(3,5-dioxomorpholin-4-yl)propylcarbamate (15g) in dry ether (150mL) was added a saturated solution of dry HCl (gas) in diethylether (300mL) at 0°C and the solution was then slowly warmed up to r.t. The precipitate obtained was filtered, washed with cold ether and dried under vaccum to give 11g of the title compound (94%). ^{1}H NMR (DMSO-d_6) δ 8.08 (br s, 3H exchangeable), 4.42 (s, 4H), 3.70 (t, J = 7.1Hz, 2H), 2.79-2.72 (m, 2H), 1.84-1.74 (m, 2H).

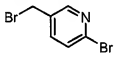
Procedure B

Intermediate 7: 2-[6-morpholin-4-yl-pyridin-3-yl]ethanamine

Step 1: 2-Bromopicoline

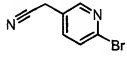
To a stirred solution of 2-amino-5-picoline (120g, 1.10mol) in 1.5L of 48% HBr was added 160mL of Br_2 (498g, 3.1mol) at –20°C over a period of 1h and then allowed to stir at same temperature for 2h. To this mixture was added slowly a solution of $NaNO_2$ (204g, 2.95mol, in 300mL of water) and the resuting solution was allowed to stir for another 1h at -20°C. The reaction mixture was quenched at –20°C by addition of aqueous NaOH (1.2Kg of NaOH in 2L of water) then extracted with diethyl ether (3x1L). The organic layer was washed with water, brine, dried with Na_2SO_4 and concentrated to give a crude residue. After purification by distillation (bath temp. 130°C, vacuum temp. 85-90°C, vacuum=0.01mm), 172g 2-bromopicoline were obtained as off white low melting solid (90%). [TLC, R_f= 0.8, diethyl ether]

Step 2: 2-Bromo-5-bromomethylpyridine



To a suspension of 2-bromo-5-methylpyridine (170g, 0.95mol) in CCl_4 (2L) was added NBS (193g, 1.08mol) and benzoylperoxide (15g) and the mixture was refluxed for 6h. The reaction mixture was cooled down to rt and the solid formed was filtered off. The filtrate was concentrated affording 275g of crude 2-bromo-5-bromomethylpyridine which was used without further purification in the next step (mixture of mono-bromo and di-bromo). [TLC, R_f= 0.7, pet. ether/ethylacetate 9:1].

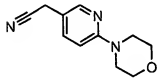
Step 3: (6-Bromopyridin-3-yl) acetonitrile



To a stirred solution of NaCN (117g, 2.38mol) in dioxane (1L) and water (1L), was added the above crude 2-bromo-5-bromomethylpyridine (275g) and the mixture was stirred at rt

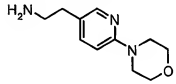
for 15h. The reaction mixture was quenched with cold water (15L) and extracted with EtOAc (3x1L). The organic layer was washed with water (3x1L), brine (2x1L), dried with Na_2SO_4 and concentrated under reduced pressure to give crude title compound. The crude residue was purified by column chromatography over silica gel (pet. ether/ethylacetate, 7:3) to give 95g (6-bromopyridin-3-yl) acetonitrile as a pale yellow solid (49%). [TLC, $R_f = 0.5$, pet. ether/ethylacetate 7:3]

Step 4: (6-Morpholin-pyridin-3-yl) acetonitrile



A mixture of (6-bromopyridin-3-yl) acetonitrile (30g, 0.15mol) and morpholin (100mL) was heated to 120°C for 4h. After completion of the reaction, the morpholin was distilled off under reduce pressure to give crude product which was purified by column chromatography (pet. ether/ethylacetate, 7:3) to give 18g (6-morpholin-pyridin-3-yl) acetonitrile as yellow solid (58%). [TLC, $R_f = 0.6$, pet. ether/EtOAc 6:4]

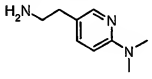
Step 5: 2-(6-Morpholin-4-yl pyridin-3-yl)-ethanamine



To a solution of (6-morpholin-pyridin-3-yl) acetonitrile (16g, 0.078mol) in MeOH (200mL) and 25% NH_4OH solution (150mL) was added Raney-Ni (20g wet) in MeOH (100mL) and the mixture was hydrogenated under 5Kg of pressure for 18h at rt using a parr- shaker. The reaction mixture was filtered through celite, washed with methanol (2x200mL) and the combined filtrate was concentrated under reduced pressure to give a crude residue. It was purified by column chromatography over silica gel ($CHCl_3$/MeOH, 4:1) to give 9g of 2-(6-morpholin-4-yl pyridin-3-yl)-ethanamine as a low melting solid (54%). [TLC, $R_f = 0.15$, $CHCl_3$/MeOH 4:1]

^{1}H NMR (DMSO-d_6) δ 8.02-7.95 (m, 1H), 7.47-7.38 (m, 1H), 6.79-6.72 (m, 1H), 3.75-3.62 (m, 4H), 3.40-3.33 (m, 4H), 2.85-2.63 (m, 4 H [2+2]), 2.60-2.45 (m, 2H); MS (ES+) 208.4.

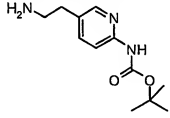
Intermediate 8: 2-(N,N-dimethylamino)-5-aminoethyl pyridine



Following the general strategies and protocols outlined in the procedure B, the title compound was obtained from the coresponding starting materials (Y: Step 1: 86%, Steps 2/3/4/5: 22%).

^{1}H NMR (DMSO-d_6) δ 7.95-7.89 (m, 1H), 7.40-7.32 (m, 1H), 6.60-6.55 (m, 1H), 2.97 (s, 6H), 2.75-2.65 (m, 2H), 2.55-2.45 (m, 2H), 1.90-1.60 (brs, 2H, exchangeable); MS (ES+) 166.

Intermediate 9: ((tert-butoxy)-N-)5-aminoetyl)(2-pyridyl)carboxamide



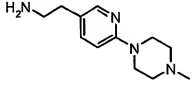
Step 1: (tert-butoxy)-N-(5-metyl-(2-pyridyl))carboxamide

To a solution of 2-amino-5-picoline (27g, 250 mmol) in DCM (250 mL) were added DMAP (4.6g, 37.5 mmol) and Boc anhydride (65.5g, 300 mmol). The reaction mixture was allowed to stirr at rt for 16h, then the solvent was removed under reduced pressure. The residue obtained was recrystallized from ACN to give 24g of (tert-butoxy)-N-(5-metyl-(2-pyridyl))carboxamide (44%).

Following the general strategies and protocols outlined in the procedure B (Steps 2 to 4; Step 2: 73%, step 3: 93%, Step 4: 77%), the title compound was obtained from the corresponding starting materials as a white solid.

^{1}H NMR ($CDCl_3$) δ 9.45 (s, 1H), 8.21 (d, J = 1.8 Hz, 1H), 7.94 (d, J = 8.7Hz, 1H), 7.52 (dd, J = 8.4 and 2.4 Hz, 1H), 2.94 (t, J = 6.9 Hz, 2H), 2.68 (t, J = 6.9 Hz, 2H), 1.55 (s, 9H), 1.14 (brs, 2H); MS (ES+) 237.9.

Intermediate 10: 2-[6-(4-methylpiperazin-1-yl-pyridin-3-yl]ethanamine

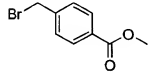


Following the general strategies and protocols outlined in the procedure B, the title compound was obtained from the corresponding starting materials as a thick liquid (Y: Steps 1/2/3/4: 51%, Step5: 69%).

^{1}H NMR (DMSO-d_6) δ 7.98-7.92 (m, 1H), 7.45-7.35 (m, 1H), 6.79-6.70 (m, 1H), 3.90-3.75 (m, 2H), 3.45-3.35 (m, 4H), 2.85-2.63 (m, 2H), 2.60-2.48 (m, 2H), 2.41-2.32 (m, 4H), 2.19 (s, 3H); MS (ES+) 221.4.

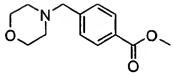
Intermediate 11: 4-morpholinomethylbenzyl alcohol

Step 1: Synthesis of methyl 4-bromomethylbenzoate.



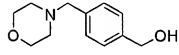
To a suspension of 150 g of methyl p-toluate and 195.5 g of NBS in CCl_4 (1.67L) under N_2 at 50°C was added portion wise over 30 min, solid benzoyl peroxide (5.0 g). No exothermic reaction was observed. After heating for 2 hours at 50°C, the yellow solution was heated up at 65°C for 1d. After cooling down to rt, the precipitate formed was filtered off and washed with 150mL of CCl_4 and the filtrate was concentrated to afford a yellow oil that solidified on standing. The title compound, containing a small fraction of starting material was used in the next step without further purification.

Step 2: Synthesis of methyl 4-morpholinomethylbenzoate.



To a solution of 66.6 g of morpholine and 269mL of triethylamine in 1.5 L of abs. EtOH under N_2 at 0°C was added dropwise over 30 min a solution of methyl 4-bromomethylbenzoate in 450mL of abs. EtOH. The resulting solution was stirred at 0°C for 2 h then slowly warmed up to rt over 4 h and stirred at rt overnight. The HPLC showed no unreacted methyl 4-bromomethylbenzoate but the remaining methyl p-toluate from the previous reaction. The solvent was removed under reduced pressure and the residue was taken up in 2 L of 1.5 N HCl. The acidic phase was washed with 3x350mL of diethyl ether then with 1x350mL of EtOAc and was neutralized to pH 7 with NaOH and then to pH 7.5 with 10% $NaHCO_3$ in water. The product was extracted with 3x700mL of EtOAc. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduce pressure, affording an orange oil. The excess EtOAc was removed by toluene distillation. The title compound was used in the next step without further purification.

Step 3: Synthesis of 4-morpholinomethylbenzyl alcohol.



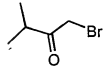
To a suspension of 33.9 g of LAH in 1.6L of dry THF under N_2 at 0°C was added drop wise a solution of methyl 4-methylmorpholinobenzoate in 233mL of dry THF over 30 min. The temperature remained under 15°C during the addition. The reaction was allowed to stir at rt overnight. It was then cooled to 0°C and quenched with 220mL of 10% aqueous NaOH. The NaOH was added drop wise (over 30 min) keeping the temperature below 10°C. It was then warmed up to rt and stirred for 2 h. The precipitate formed was filtered off and washed with 200mL of THF. The filtrate was concentrated affording a white solid that was taken up in EtOAc (1L) and heated up at 65°C for 45 min then cooled down to rt. The EtOAc solution was washed with brine (250mL). Then 700mL of the solvent were removed to give a suspension of the product and 300mL of hexane were added. The

solution was cooled down to 4°C and held for 12 h. The crystals were filtered off and washed with a cold 1:1 mixture of EtOAc/:hexane (200mL) then dried at 40°C under vacuum overnight, affording 107.5 g of the title compound as white crystals (52% yield from methyl p-toluate).

Intermediate 12: 1-bromoacetone

In a 100 mL flask, 1-bromo-2,2-dimethoxy-propane (7.3 mmol, 1.02 ml) was added to a solution of HCl (1M; 5.2 mL) in EtOH (47 mL). The solution was left stirring at r.t for 3 days. The pH was brought to 7 with Et_3N and the solution was used as such in the next step

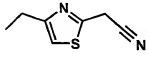
Intermediate 13: 1-Bromo-3-methyl-2-butanone



To a solution of 3-methyl-2-butanone (43g, 0.5mol) in dry methanol (300mL) at 0°C was added Br_2 (80g, 0.5mol) slowly at the same temperature and then allowed to stir at 10°C for 1h. The reaction mixture became colourless, then quenched with water (150mL) and allowed to stir at rt for 20h. The reaction mixture was further diluted with water (450mL) and extracted with diethylether (2x500mL). The ether layer was washed with water, 10% aqueous K_2CO_3 solution, water, brine and dried with Na_2SO_4. The solvent was removed at rt to give 67g of 1-bromo-3-methyl-2-butanone as a liquid (75%).

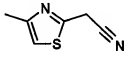
Procedure C

Intermediate 14: (4-ethyl-1,3-thiazol-2-yl)acetonitrile



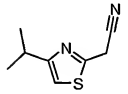
To a solution of 1-bromo-2-butanone (10.3g, 57.98 mmol) in EtOH (200 mL) were added 2-cyanothioacetamide (5.8 g, 57.98 mmol) and triethylamine (1.59 mL, 11.6 mmol) and the solution was stirred under reflux for 1h. After cooling down to r.t., the solvent was removed. The orange solid obtained was washed with AcOEt then cyclohexane, and recrystallized from EtOH to afford 7.2 g of the title compound as orange needles (Y= 81%).
^{1}H NMR (CD_3OD) δ 7.56 (t, J = 0.75Hz, 1H), 4.91 (s, 2H), 2.89 (dq, J = 0.75Hz, J = 7.54Hz, 2H), 1.34 (t, J = 7.54Hz, 3H).
HPLC (max plot) 98%; Rt: 1.66 min

Intermediate 15: (4-methyl-1,3-thiazol-2-yl)acetonitrile



Following the general strategies and protocols outlined in the procedure C, the title compound was obtained from 1-bromoacetone (Intermediate 12) and 2-cyanothioacetamide in the presence of triethylamine for 12 h at 90°C in EtOH (76.4%).
^{1}H NMR (DMSO-d_6) δ 7.32 (d, J =1.13 Hz, 1H), 4.5 (s, 2H), 2.39 (d, J=1.13 Hz, 3H).
^{13}C NMR (DMSO-d_6) δ 158.10 (C), 152.63 (C), 117.45 (C), 115.98 (CH), 21.71 (CH2), 16.96 (CH3)
HPLC (max plot) 90% ; Rt: 1.23 min.

Intermediate 16: (4-Isopropyl-1,3-thiazol-2-yl)acetonitrile



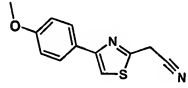
Following the general strategies and protocols outlined in the procedure C, the title compound was obtained from 1-bromo-3-methyl-2-butanone (Intermediate 13) and 2-cyanothioacetamide in the presence of triethylamine for 4 h at 90°C in EtOH

The crude was purified by flash chromatography over silica gel (5% ethylacetate in pet. Ether) (33%.as a brown liquid).

^{1}H NMR (DMSO-d_6) δ 7.27 (s, 1H), 4.52 (s, 2H), 3.04-2.99 (m, 1H), 1.26 (d, J= 6.8Hz, 6H).

M^-(ES): 165.4; M^+(ES): 167.4.

Intermediate 17: [4-(4-methoxyphenyl)-1,3-thiazol-2-yl]acetonitrile

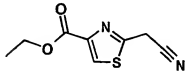


Following the general strategies and protocols outlined in the procedure C, the title compound was obtained from 2-bromo-4'-methoxyacetophenone and 2-cyanothioacetamide in the presence of triethylamine for 2 h at 90°C in EtOH (71.4%).

^{1}H NMR ($CDCl_3$) δ 7.75 (d, J=9.04 Hz, J=4.9 Hz, 2H), 7.19 (s, 1H), 6.89 (d, J=8.67Hz, J=4.9 Hz, 2H), 4.14 (s, 1H), 3.79 (s, 3H), 1.73 (H2O, 2.64H)-13C (ppm, CDCl3, 300 MHz):160.32 (C), 157.45 (C), 156.41 (C), 128.10 (CH), 126.97 (C), 115.81 (C), 114.60 (CH), 112.57 (CH), 55.75 (CH3), 22.88 (CH2)

M^-(ES): 229; M^+(ES): 231; HPLC (max plot) 96.4% ; Rt: 3.27 min.

Intermediate 18: ethyl 2-(cyanomethyl)-1,3-thiazole-4-carboxylate

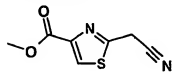


Following the general strategies and protocols outlined in the procedure C using microwave technology, the title compound was obtained from ethyl-bromopyruvate and 2-cyanothioacetamide in the presence of triethylamine for 2 min at 155°C in EtOH (54.3%).

^{1}H NMR (DMSO-d_6) δ 8.53 (s, 1H); 4.62 (s, 2H); 4.31 (q, J=7.2Hz, 2H), 1.30 (t, J=7.2Hz, 3H)

M^-(ES): 195; M^+(ES): 197; HPLC (max plot) 100% ; Rt: 1.56 min.

Intermediate 19: methyl 2-(cyanomethyl)-1,3-thiazole-4-carboxylate

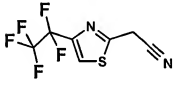


Following the general strategies and protocols outlined in the procedure C using microwave technology, the title compound was obtained from methyl-bromopyruvate and 2-cyanothioacetamide in the presence of triethylamine for 2.5 min at 145°C in MeOH (35.9%).

^{1}H NMR (DMSO-d_6) δ 8.54 (s, 1H); 4.61(s, 2H); 3.83 (s, 3H)

M^-(ES): 183; M^+(ES): 181; HPLC (max plot) 100% ; Rt: 1.09 min.

Intermediate 20: [4-(pentafluoroethyl)-1,3-thiazol-2-yl]acetonitrile

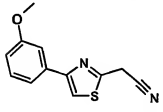


Following the general strategies and protocols outlined in the procedure C, the title compound was obtained from 1-bromo-3,3,4,4,4-pentafluoro-2-butanone and 2-cyanothioacetamide in the presence of triethylamine for 12 h at 80°C in EtOH (26.6%).

^{1}H NMR (CDCl3) δ 7.87 (s, 1H), 4.20 (s, 2H).

M^-(ES): 241; HPLC (max plot) 82% ; Rt: 3.20 min.

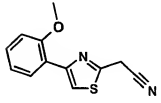
Intermediate 21: [4-(3-methoxyphenyl)-1,3-thiazol-2-yl]acetonitrile



Following the general strategies and protocols outlined in the procedure C, the title compound was obtained from 2-bromo-3'methoxyacetophenone and 2-cyanothioacetamide in the presence of triethylamine for 1 h at reflux in EtOH (99%).

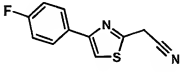
^{1}H NMR (DMSO-d_6) δ 8.16 (s, 1H), 7.54-7.48 (m, 2H), 7.39-7.33 (m, 1H), 6.95-6.91 (m, 1H), 4.62 (s, 2H), 3.81 (s, 3H).
HPLC (max plot) 88% ; Rt: 3.18 min

Intermediate 22: [4-(2-methoxyphenyl)-1,3-thiazol-2-yl]acetonitrile



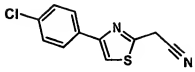
Following the general strategies and protocols outlined in the procedure C, the title compound was obtained from 2-bromo-2'methoxyacetophenone and 2-cyanothioacetamide in the presence of triethylamine for 1 h at reflux in EtOH (79.6%).
^{1}H NMR (DMSO-d_6) δ 8.12 (dd, J = 1.9Hz, 7.9Hz, 1H), 8.08 (s, 1H), 7.38-7.32 (m, 1H), 7.16-7.13 (m, 1H), 7.08-7.02 (m, 1H), 4.61 (s, 2H), 3.92 (s, 3H).
M^+(ES): 231.3; HPLC (max plot) 96.7% ; Rt: 3.35 min

Intermediate 23: [4-(4-fluorophenyl)-1,3-thiazol-2-yl]acetonitrile



Following the general strategies and protocols outlined in the procedure C, the title compound was obtained from 2-bromo-4'fluoroacetophenone and 2-cyanothioacetamide in the presence of triethylamine for 1 h at reflux in EtOH (83.2%).
^{1}H NMR (DMSO-d_6) δ 8.12 (s, 1H), 8.01-7.97 (m, 2H), 7.31-7.25 (m, 2H), 4.62 (s, 2H).
M^+(ES): 219.2; HPLC (max plot) 97.4% ; Rt: 3.22 min

Intermediate 24: [4-(4-chlorophenyl)-1,3-thiazol-2-yl]acetonitrile

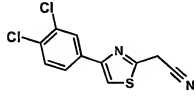


Following the general strategies and protocols outlined in the procedure C, the title compound was obtained from 2-bromo-4'-chloroacetophenone and 2-cyanothioacetamide in the presence of triethylamine for 1h 30 at reflux in EtOH (82.6%).

^{1}H NMR (CDCl3) δ 7.84(d, J = 8.67Hz, 2H) ,7.48 (s, 1H) ; 7.42 (d, J = 8.67Hz, 2H,), 4.19 (s, 2H).

M^-(ES): 233; M^+(ES): 235; HPLC (max plot) 99.2% ; Rt: 3.80 min.

Intermediate 25: [4-(3,4-dichlorophenyl)-1,3-thiazol-2-yl]acetonitrile

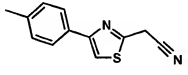


Following the general strategies and protocols outlined in the procedure C, the title compound was obtained from 3,4-dichlorophenacyl bromide and 2-cyanothioacetamide in the presence of triethylamine for 1h 30 at Reflux in EtOH (76.4%).

^{1}H NMR (DMSO-d_6) δ 8.34 (s, 1H), 8.2 (d, J = 2.26Hz, 1H), 7.99 (dd, J = 8.29Hz, J = 2.27Hz, 1H), 7.78 (d, J = 8.29Hz, 1H), 4.64 (s, 2H).

HPLC (max plot) 95.2% ; Rt: 4.18 min.

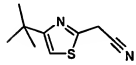
Intermediate 26: [4-(4-methylphenyl)-1,3-thiazol-2-yl]acetonitrile



Following the general strategies and protocols outlined in the procedure C, the title compound was obtained from 4-methylphenacyl bromide and 2-cyanothioacetamide in the presence of triethylamine for 1h 30 at reflux in EtOH (83%).

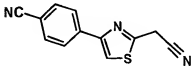
^{1}H NMR (DMSO-d_6) δ 8.05 (s, 1H), 7.85 (d, J = 7.91Hz, 2H), 7.27 (d, J = 7.91Hz, 2H), 4.62 (s, 2H), 2.33 (s, 3H)
M^-(ES): 213.2; M^+(ES): 215.3; HPLC (max plot) 100% ; Rt: 3.59 min.

Intermediate 27 : (4-tert-butyl-1,3-thiazol-2-yl)acetonitrile



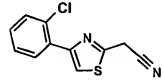
Following the general strategies and protocols outlined in the procedure C, the title compound was obtained from 1-bromopinacolone and 2-cyanothioacetamide in the presence of triethylamine for overnight at r.t. in EtOH (87%).
^{1}H NMR (DMSO-*d6*) δ 7.27 (s, 1H), 4.51 (s, 2H), 1.27 (s, 9H)
HPLC (max plot) 100% ; Rt: 2.98 min.

Intermediate 28 : 4-[2-(cyanomethyl)-1,3-thiazol-4-yl]benzonitrile



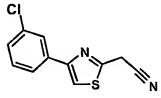
Following the general strategies and protocols outlined in the procedure C, the title compound was obtained from 2-bromo-4'-cyano acetophenone and 2-cyanothioacetamide in the presence of triethylamine for 1h30 at reflux in EtOH (84.4%).
^{1}H NMR (DMSO-d_6) δ 8.41 (s, 1H), 8.16-8.13 (m, 2H), 7.94-7.91 (m, 2H), 4.65 (s, 2H).
M^+(ES): 226.3; HPLC (max plot) 99.1% ; Rt: 3.00 min.

Intermediate 29: [4-(2-chlorophenyl)-1,3-thiazol-2-yl]acetonitrile



Following the general strategies and protocols outlined in the procedure C, the title compound was obtained from 2-chlorophenacyl bromide and 2-cyanothioacetamide in the presence of triethylamine for 1h30 at reflux in EtOH (78.6%).
^{1}H NMR (DMSO-d_6) δ 8.10 (s, 1H), 7.86-7.83 (m, 1H), 7.59-7.56 (m, 1H), 7.48-7.38 (m, 2H), 4.63 (s, 2H).
M$^-$(ES): 233.2; M$^+$(ES): 235.2; HPLC (max plot) 100% ; Rt: 3.47 min.

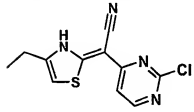
Intermediate 30: [4-(3-chlorophenyl)-1,3-thiazol-2-yl]acetonitrile



Following the general strategies and protocols outlined in the procedure C, the title compound was obtained from 3-chlorophenacyl bromide and 2-cyanothioacetamide in the presence of triethylamine for 1h30 at reflux in EtOH (82.5%).
^{1}H NMR (DMSO-d_6) δ 8.28 (s, 1H), 8.00 (t, J = 1.5Hz, 1H), 7.92 (dt, J = 7.5Hz, J = 1.5Hz, 1H), 7.49 (t, J = 7.9Hz, 1H), 7.44-7.40 (m, 1H), 4.63 (s, 2H).
M$^-$(ES): 233.2; M$^+$(ES): 235.2; HPLC (max plot) 99.3% ; Rt: 3.77 min.

Procedure D

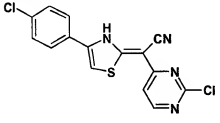
Example 1: (2-chloropyrimidin-4-yl)-(4-ethyl-3H-thiazol-2ylidene)-acetonitrile



To a suspension of LiH (699 mg, 87.90 mmol) in anhydrous THF was added dropwise a suspension of (4-ethyl-1,3-thiazol-2-yl)acetonitrile (6.69g, 43.95 mmol) in THF (60mL) and the suspension was stirred for 1h at O°C. A suspension of 2,4-dichloropyrimidine

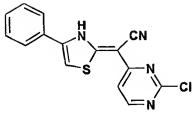
(7.2g, 48.34 mmol) in THF (60mL) was added dropwise to the pale red suspension at 0°C and the resulting mixture was stirred at rt for 7h. The reaction was quenched by addition water (10mL) at 0°C then the solution obtained was left overnight under stirring. The THF was removed under reduced pressure then 80 mL of water were added and the suspension was acidified with 1N HCl. The precipitate formed was filtered off and washed with water until neutral pH to afford 9.96g of the title compound as a beige powder (Y = 85.5%).
^{1}H NMR (DMSO-d_6) δ 12.97 (br s, 1H), 8.23 (d, J = 5.7Hz, 1H), 7.05 (d, J = 5.7Hz, 1H), 6.87 (s, 1H), 2.66 (q, J = 7.5Hz, 2H), 1.19 (t, J = 7.5Hz, 3H).
M^-(ES): 263.2; M^+(ES): 265.2; HPLC (max plot) 99.6% ; Rt: 3.28 min.

Example 2: [4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-chloropyrimidin-4-yl)acetonitrile



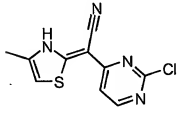
Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from (4-(4-chlorophenyl)-1,3-thiazol-2-yl)acetonitrile and 2,4-dichloropyrimidine in the presence of NaH overnight at 60°C. in THF (70%).
^{1}H NMR (DMSO-*d6*) δ 7.92 (d, J = 8.5 Hz, 2H); 7.79 (m, 2H); 7.52 (d, J = 8.5 Hz, 2H); 6.79 (br d, 1H);
M^+(ES): 346.9; HPLC (max plot) 99 %, Rt. 4.30 min.

Example 3: Preparation of (2-chloropyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



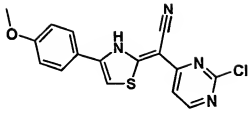
Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from (4-phenyl-1,3-thiazol-2-yl)acetonitrile and 2,4-dichloropyrimidine in the presence of NaH for 4 **d** at 70°C. in THF (66%).
^{1}H NMR (DMSO-*d6*) δ 7.92 (br d,1H), 7.85 (d, *J* = 7.1 Hz, 2H), 7.69-7.37 (m, 3H), 6.89 (br d, 1H), M^+(ES): 313; HPLC (max plot) 98% ; Rt. 4.72 min.

Example 4: (2-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from (4-methyl-1,3-thiazol-2-yl)acetonitrile and 2,4-dichloropyrimidine in the presence of NaH for 5h at r.t. in THF. A purification step was performed using aminomethyl polystyrene resin in DMA at 70°C allowing to specifically remove the regioisomer resulting from the displacement of the chlorine in the 2 position of the pyrimidine (69.6%).
^{1}H NMR (MeOD + NaOD) δ 7.62 (d, *J* = 6.03Hz, 1H), 6.72 (d, *J* = 6.03Hz, 1H9, 6.55 (d, *J* = 0.75Hz, 1H), 2.31 (d, *J* = 0.75Hz, 3H).
M^-(ES): 249; M^+(ES): 251; HPLC (max plot) 96% ; Rt: 2.90 min.

Example 5: (2-chloropyrimidin-4-yl)[4-(4-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile

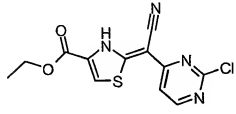


Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from [4-(4-methoxyphenyl)-1,3-thiazol-2-yl]acetonitrile and 2,4-dichloropyrimidine in the presence of NaH for 24 h at r.t. in THF (94.4%).

^{1}H NMR (DMSO-d_6) δ 8.01 (br s, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.49 (s, 1H), 7.03 (d, J = 8.3Hz, 2H), 6.92 (br s, 1H), 3.79 (s, 3H).

M^-(ES): 341; M^+(ES): 343; HPLC (max plot) 100% ; Rt: 4.40 min.

Example 6: ethyl-2-[(2-chloropyrimidin-4-yl)(cyano)methylene]-2,3-dihydro-1,3-thiazole-4-carboxylate

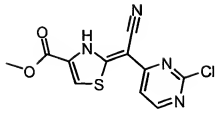


Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from ethyl 2-(cyanomethyl)-1,3-thiazole-4-carboxylate and 2,4-dichloropyrimidine in the presence of LiH for overnight at 0°C to r.t. in THF (80%).

^{1}H NMR (DMSO-d_6) δ 7.88 (s,1H), 7.71 (d, J=6Hz, 1H), 6.78(d, J=6Hz, 1H), 3.61 (q, J=7.16Hz, 2H), 1.18 (t, J=7.15Hz, 3H)

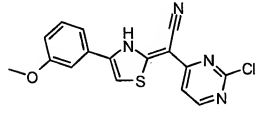
M^-(ES): 307; M^+(ES): 309; HPLC (max plot) 99% ; Rt: 3.44 min.

Example 7: methyl-2-[(2-chloropyrimidin-4-yl)(cyano)methylene]-2,3-dihydro-1,3-thiazole-4-carboxylate



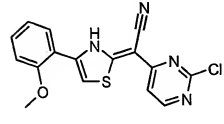
Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from methyl 2-(cyanomethyl)-1,3-thiazole-4-carboxylate and 2,4-dichloropyrimidine in the presence of LiH for 36 h at 0° to r.t. in THF (46.3%).
^{1}H NMR (DMSO-d_6) δ 8.16 (s,1H); 7.68 (br s,1H); 6.68 (br s, 1H); 3.77 (s,3H)
M^-(ES): 293; M^+(ES): 295; HPLC (max plot) 99% ; Rt: 2.93 min.

Example 8: (2-chloropyrimidin-4-yl)[4-(3-methoxyphenyl)-1,3-thiazol-2-yl]acetonitrile



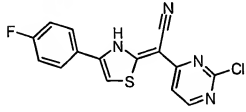
Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from [4-(3-methoxyphenyl)-1,3-thiazol-2-yl]acetonitrile and 2,4-dichloropyrimidine in the presence of LiH for overnight at r.t. in THF (68%).
^{1}H NMR (DMSO-d_6) δ 8.05-7.85 (br d, 1H), 7.73 (s, 1H), 7.41-7.36 (m, 3H), 6.98-6.96 (m, 1H), 6.90 (br d, 1H), 3.82 (s, 3H).
HPLC (max plot) 97%; Rt: 4.32 min.

Example 9: (2-chloropyrimidin-4-yl)[4-(2-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile



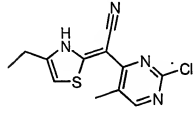
Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from [4-(2-methoxyphenyl)-1,3-thiazol-2-yl]acetonitrile and 2,4-dichloropyrimidine in the presence of LiH for overnight at 0°C to r.t. in THF (72.9%).
^{1}H NMR (DMSO-d_6) δ 13.45 (br s, 1H), 8.38-8.04 (m, 1H), 7.71-7.44 (m, 3H), 7.23-7.02 (m, 3H), 3.93 (s, 3H)..
M^+(ES): 343.2; HPLC (max plot): 98.1%; Rt: 4.32 min.

Example 10: (2-chloropyrimidin-4-yl)[4-(4-fluorophenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile



Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from [4-(4-fluorophenyl)-1,3-thiazol-2-yl]acetonitrile and 2,4-dichloropyrimidine in the presence of LiH for overnight at 0°C to r.t. in THF (60.7%).
^{1}H NMR (DMSO-d_6) δ 7.94-7.89 (m, 4H), 7.70 (s, 1H), 7.33-7.27 (m, 2H), 6.85 (br d, 1H).
M^+(ES): 331.1; HPLC (max plot) 99.2%; Rt: 4.20 min.

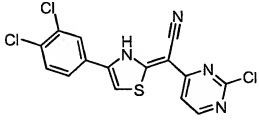
Example 11: (2-chloro-5-methylpyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from (4-ethyl-1,3-thiazol-2-yl)acetonitrile and 2,4-dichloro-5-methylpyrimidine in the presence of LiH for 4 h at 0°C to r.t. in THF (60.4%).

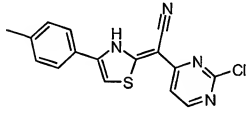
^{1}H NMR (DMSO-d_6) δ 12.72 (br s, 1H), 8.02 (s, 1H), 6.85 (s, 1H), 2.71-2.63 (m, 2H), 2.41 (d, J = 0.7Hz, 3H), 1.18 (t, J = 7.5Hz, 3H).
M^-(ES): 277.1; M^+(ES): 279.2; HPLC (max plot) 95.2%; Rt: 3.66 min.

Example 12: (2-chloropyrimidin-4-yl)[4-(3,4-dichlorophenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile



Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from [4-(3,4-dichlorophenyl)-1,3-thiazol-2-yl]acetonitrile and 2,4-dichloropyrimidine in the presence of LiH for overnight at r.t. in THF (69.6%).
^{1}H NMR (DMSO-d_6) δ 8.16 (s, 1H), 7.98 (s, 1H), 7.92 (d, J = 7.54Hz, 1H), 7.72 (d, J = 8.29Hz, 2H), 6.77 (s, 1H)
M^-(ES): 381; M^+(ES): 382.9; HPLC (max plot) 100% ; Rt: 4.76 min.

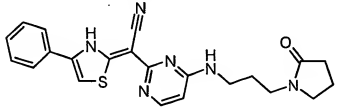
Example 13: (2-chloropyrimidin-4-yl)[4-(4-methylphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile



Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from [4-(4-methylphenyl)-1,3-thiazol-2-yl]acetonitrile and 2,4-dichloropyrimidine in the presence of LiH for overnight at r.t. in THF (69.5%).
^{1}H NMR (DMSO-d_6) δ 8.05 (s, 1H), 7.73 (d, J = 7.16Hz, 2H), 7.61 (s, 1H), 7.29 (d, J = 7.53Hz, 2H), 6.92 (br s, 1H), 2.35 (s, 3H)

M^-(ES): 325.2; M^+(ES): 327.1; HPLC (max plot) 97% ; Rt: 4.58 min.

Example 14: (4-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-2-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

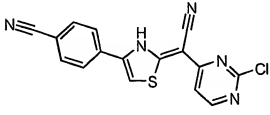


Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from (4-phenyl-1,3-thiazol-2-yl)acetonitrile and 1-{3-[(2-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one in the presence of sodium hydride for overnight at 50°C in THF as a light yellow powder (19%).

^{1}H NMR (DMSO-d_6) δ 12.75 (br s, 1H), 8.15-8.00 (m, 1H), 7.81-7.65 (m, 2H), 7.40-7.33 (s, 1H), 7.23-7.08 (m, 3H), 5.73 (d, J = 7.1Hz, 1H), 3.15-3.01 (m, 6H), 2.00-1.95 (m, 2H), 1.72-1.48 (m, 4H).

M^+(ES): 419.4; HPLC (max plot) 99% ; Rt: 2.63 min.

Example 15: 4-{2-[(2-chloropyrimidin-4-yl)(cyano)methylene]-2,3-dihydro-1,3-thiazol-4-yl}benzonitrile

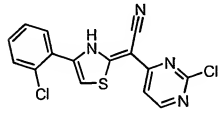


Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from 4-[2-(cyanomethyl)-1,3-thiazol-4-yl]benzonitrile and 2,4-dichloropyrimidine in the presence of LiH for overnight at r.t. in THF (65.3%).

^{1}H NMR (DMSO-d6) δ 8.12 (d, J = 8.6Hz, 2H), 8.05 (s, 1H), 7.9(d, J = 8.6Hz, 2H), 7.72 (br d, 1H), 6.73 (br d, 1H).

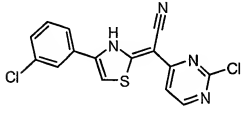
M^-(ES): 336.1; M^+(ES): 338.2; HPLC (max plot) 99.8% ; Rt: 3.96 min.

Example 16: [4-(2-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-chloropyrimidin-4-yl)acetonitrile



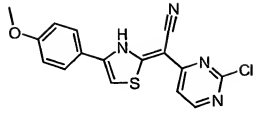
Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from [4-(2-chlorophenyl)-1,3-thiazol-2-yl]acetonitrile and 2,4-dichloropyrimidine in the presence of LiH for overnight at r.t. in THF (65.2%).
^{1}H NMR (DMSO-d6) δ 8.08 (s, 1H), 7.59 (m, 3H), 7.48 (m, 3H), 6.97 (s, 1H).
M^-(ES): 347; M^+(ES): 348.9; HPLC (max plot) 100% ; Rt: 4.32 min.

Example 17: [4-(3-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-chloropyrimidin-4-yl)acetonitrile



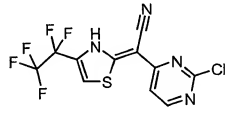
Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from [4-(3-chlorophenyl)-1,3-thiazol-2-yl]acetonitrile and 2,4-dichloropyrimidine in the presence of LiH for overnight at r.t. in THF (41.2%).
^{1}H NMR (DMSO-d6) δ 7.9 (m, 5H), 7.46 (m, 2H), 6.81 (s, 1H).
M^-(ES): 346.9; M^+(ES): 348; HPLC (max plot) 99.6% ; Rt: 4.51 min.

Example 18: (2-chloropyrimidin-4-yl)[4-(4-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile



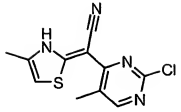
Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from [4-(4-methoxyphenyl)-1,3-thiazol-2-yl]acetonitrile and 2,4-dichloropyrimidine in the presence of NaH for 24h at r.t.°C in THF (94.4%).
^{1}H NMR (MeOD+NaOD aq) δ 7.83 (d, *J*=9.04 Hz, 2H), 7.63 (d, *J*=6.4 Hz, 1H), 7.13 (s, 1H), 6.94 (d, *J*=8.67 Hz, 2H), 6.76 (d, *J*=6.03 Hz, 1H), 3.82 (s, 3H)
M^+(ES): 343; HPLC (max plot) 94% ; Rt: 4.40 min.

Example 19: (2-chloropyrimidin-4-yl)[4-(pentafluoroethyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile



Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from [4-(pentafluoroethyl)-1,3-thiazol-2-yl]acetonitrile and 2,4-dichloropyrimidine in the presence of LiH for 4 d at 0°C to r.t. in THF. A purification step was performed using aminomethyl polystyrene resin in DMA at 70°C allowing to specifically remove the regioisomer resulting from the displacement of the chlorine in the 2 position of the pyrimidine (55.8%).
^{1}H NMR (DMSO-d6) δ14.5 (br s, 1H), 7.85 (d, *J*=6.4Hz, 1H), 7.64 (s, 1H), 6.97 (s, 1H)
HPLC (max plot) 85% ; Rt: 4.04 min.

Example 20: (2-chloro-5-methylpyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

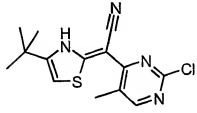


Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from (4-methyl-1,3-thiazol-2-yl)acetonitrile and 2,4-dichloro-5-methylpyrimidine in the presence of LiH for 2 d at 0°C to r.t. in THF. A purification step was performed using aminomethyl polystyrene resin in DMA at 70°C allowing to specifically remove the regioisomer resulting from the displacement of the chlorine in the 2 position of the pyrimidine (72.7%).

^{1}H NMR (DMSO-d6) δ12.71(s,1H), 8.04 (s,1H), 6.86 (d, *J*= 1.1Hz,1H), 2.43 (s,3H), 2.30 (d, *J*= 1.1Hz,3H)

M^+(ES): 265; HPLC (max plot) 97% ; Rt: 3.12 min.

Example 21: (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-chloro-5-methylpyrimidin-4-yl)acetonitrile

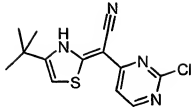


Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from (4-tert-butyl-1,3-thiazol-2-yl)acetonitrile and 2,4-dichloro-5-methylpyrimidine in the presence of NaH for 2.5 d at r.t. in THF (92.3%).

^{1}H NMR (DMSO-d6) δ 13.58 (br s, 1H), 8.09 (s, 1H), 6.93 (s, 1H), 2.40 (s, 3H), 1.34 (s, 9H).

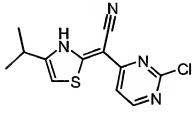
HPLC (max plot) 98.5%.

Example 22: (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-chloropyrimidin-4-yl)acetonitrile



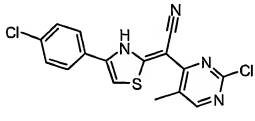
Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from (4-tert-butyl-1,3-thiazol-2-yl)acetonitrile and 2,4-dichloropyrimidine in the presence of NaH overnight at r.t. in THF (57.8%).
^{1}H NMR (DMSO-d6) δ 13.10 (br s, 1H), 8.26 (br d, 1H), 7.03 (br d, 1H), 6.91 (s, 1H), 1.33 (s, 9H).
HPLC (max plot) 100%.

Example 23 : (2-chloropyrimidin-4-yl)(4-isopropyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



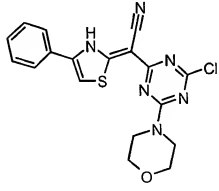
Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from (4-isopropyl-1,3-thiazol-2-yl)acetonitrile and 2,4-dichloropyrimidine in the presence of NaH overnight at 0°C to rt in THF (38.6%).
^{1}H NMR (DMSO-*d6*) δ 12.98 (s, 1H), 8.24 (d, J = 5.7Hz, 1H), 7.05 (d, J = 5.7Hz, 1H), 6.88 (d, J = 0.7Hz, 1H), 3.05 (sept., J = 6.8 Hz, 1H), 1.22 (d, J = 6.8Hz, 6H)
HPLC (max plot) 100% ; Rt: 3.82 min.

Example 24: (2-chloro-5-methylpyrimidin-4-yl)[4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile



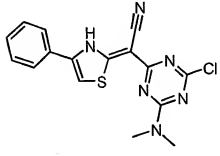
Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from [4-(4-chlorophenyl-1,3-thiazol-2-yl)]acetonitrile and 2,4-dichloro-5-methyl-pyrimidine in the presence of NaH in THF (78%).
M^+(ES): 361.2

Example 25: (4-chloro-6-morpholin-4-yl-1,3,5-triazin-2-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from (4-phenyl-1,3-thiazol-2-yl)acetonitrile and 2,4-dichloro-6-morpholin-4-yl-1,3,5-triazine in the presence of NaH in THF (99%).
M^+(ES): 399.3; LC (215nm): 44%

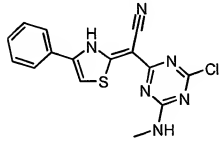
Example 26: [4-chloro-6-(dimethylamino)-1,3,5-triazin-2-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from (4-phenyl-1,3-thiazol-2-yl)acetonitrile and 4,6-dichloro-N,N-dimethyl-1,3,5-triazin-2-amine in the presence of NaH in THF (87%).

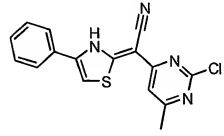
M^+(ES): 357.25; LC (215nm): 92%

Example 27: [4-chloro-6-(methylamino)-1,3,5-triazin-2-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



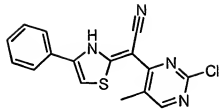
Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from (4-phenyl-1,3-thiazol-2-yl)acetonitrile and 4,6-dichloro-N-methyl-1,3,5,triazin-2-amine in the presence of NaH in THF (92%).
M^+(ES): 343; LC (215nm): 92%

Example 28: (2-chloro-6-methylpyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



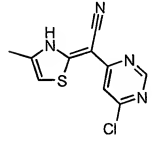
Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from (4-phenyl-1,3-thiazol-2-yl)acetonitrile and 2,4-6-methyl-pyrimidine in the presence of NaH in THF (79%).
M^+(ES): 327.27; LC (215nm): 95%

Example 29: (2-chloro-5-methylpyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



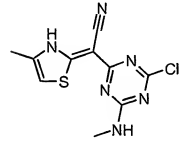
Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from (4-phenyl-1,3-thiazol-2-yl)acetonitrile and 2,4-5-methyl-pyrimidine in the presence of NaH in THF (93%).
M^+(ES): 327.27; LC (215nm): 52%

Example 30: (6-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



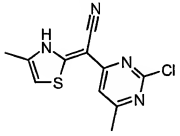
Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from (4-methyl-1,3-thiazol-2-yl)acetonitrile and 4,6-dichloropyrimidine in the presence of NaH inTHF (80%).
M^+(ES): 251.21; LC (215nm): 84%

Example 31: [4-chloro-6-(methylamino)-1,3,5-triazin-2-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



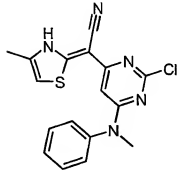
Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from (4-methyl-1,3-thiazol-2-yl)acetonitrile and 4,6-dichloro-N-methyl-1,3,5-triazin-2-amine in the presence of NaH in THF (56%).
M^+(ES): 281.26; LC (215nm): 78%

Example 32: (2-chloro-6-methylpyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



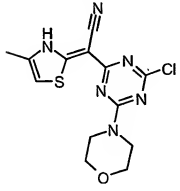
Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from (4-methyl-1,3-thiazol-2-yl)acetonitrile and 2,4-6-methyl-pyrimidine in the presence of NaH in THF (65%).
M^+(ES): 265.2; LC (215nm): 42%

Example 33: {2-chloro-6-[methyl(phenyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from (4-methyl-1,3-thiazol-2-yl)acetonitrile and 2,6-dichloro-N-methyl-N-phenylpyrimidin-4-amine in the presence of NaH in THF (83%).
M^+(ES): 356.28; LC (215nm): 95%

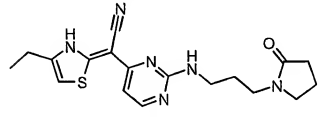
Example 34: (4-chloro-6-morpholin-4-yl-1,3,5-triazin-2-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure D, the title compound was obtained from (4-methyl-1,3-thiazol-2-yl)acetonitrile and 2,4-dichloro-6-morpholin-4-yl-1,3,5-triazine in the presence of NaH in THF (99%).
M^+(ES): 337.27; LC (215nm): 40%

Procedure E

Example 35: (4-ethyl-1,3-thiazol-2(3H)-ylidene)(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile TFA salt



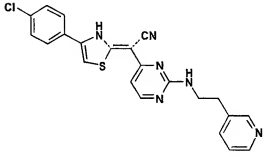
To a suspension of (2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile in EtOH in 4 microwave tubes (250 mg in each tube) were added N-(3'-aminopropyl)-2-pyrrolidinone and Et_3N and the resulting suspension was heated up to 155°C for 4 min. After cooling down to rt, the yellow precipitate formed was filtered off, washed with water (3X) and dried under vacuum at 40°C, affording 1.29g of the title compound as a yellow solid (HPLC purity : 96.8%).

The crude solid was taken up in DCM and excess TFA was added. After addition of ether a yellow precipitate formed and was filtered off then washed with ether (3X) and dried under vacuum at 40°C overnight, affording the salt form of the title compound with 97.5% purity. After purification by preparative HPLC and lyophilization, 1.3g of the title compound was obtained as a TFA salt (Y= 70.2%).

^{1}H NMR (DMSO-d_6) δ 8.06 (br s, 1H), 7.68 (d, J = 7.1Hz, 1H), 7.02 (s, 1H), 6.44 (d, J = 7.1Hz, 1H), 3.55-3.43 (m, 2H), 3.35-3.26 (m, 4H), 2.73-2.66 (m, 2H), 2.22-2.16 (m, 2H), 1.94-1.78 (m, 4H), 1.23-1.18 (m, 3H).

M^+(ES): 371.2; HPLC (max plot) 99.6% ; Rt: 2.22 min.

Example 36: [4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

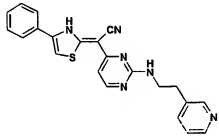


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene)acetonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine for 4d at 70°C in EtOH (20%).

1H NMR (DMSO-d6) δ 10.77 (br s, 1H), 8.76 (s, 1H), 8.71 (br d, 1H), 8.28 (d, J = 7.9 Hz, 1H), 7.97 (d, J = 8.7 Hz, 2H), 7.83 (dd, J = 7.9 Hz, J = 5.3 Hz, 1H), 7.72 (s, 1H), 7.55 (br s, 1H), 7.48 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 7.5 Hz, 1H), 6.28 (d, J = 7.5 Hz, 1H), 3.89 (br t, 2H), 3.12 (t, J = 6.8 Hz, 2H).

M^+(ES): 433.3, HPLC (max plot) 100%, Rt. 2.58 min.

Example 37: (4-phenyl-1,3-thiazol-2(3H)-ylidene){2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

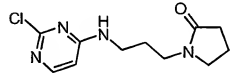


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine for 5 min at 155°C in EtOH (19%).

^{1}H NMR (DMSO-*d6*) δ 10.71 (br s, 1H), 8.75 (s, 1H), 8.70 (d, J = 5.3 Hz, 1H), 8.27 (d, *J* = 7.5 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 2H), 7.82 (dd, *J* = 7.5 Hz, *J* = 5.3 Hz, 1H), 7.65 (s, 1H), 7.52 (br s, 1H), 7.42 (d, *J* = 7.5 Hz, 2H), 7.35-7.27 (m, 2H), 6.28 (d, *J* = 7.6 Hz, 1H), 3.89 (br t, 2H), 3.12 (t, *J* = 6.8 Hz, 2H).

M^+(APCI): 399.0; HPLC (max plot) 99%, Rt. 2.08 min.

Intermediate 31: 1-{3-[(2-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one

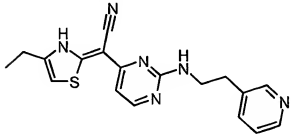


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from 2,4-dichloropyrimidine and N-(3'-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 4 h at 70°C in EtOH (50.8%).

NMR-1H (DMSO) 7.87 (m, 2H), 6.43 (br d, 1H), 3.35-3.28 (m, 4H), 3.23-3.19 (m, 2H), 2.23-2.17 (m, 2H), 1.96-1.86 (m, 2H), 1.72-1.63 (m, 2H)

HPLC (max plot) 100%.

Example 38: {2-[(3-aminopropyl)amino]pyrimidin-4-yl}(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

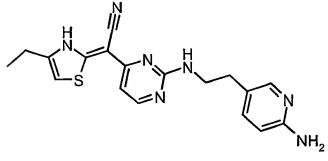


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine for 5 min at 155°C in EtOH (74%).

^{1}H NMR (DMSO-d_6) δ 7.46 (d, J = 6Hz, 1H), 6.41 (s, 1H), 6.11 (d, J = 6Hz, 1H), 3.60-3.10 (m, 2H+2H exchangeable), 2.80 (t, J = 7.1Hz, 2H), 2.56 (q, J = 7.5Hz, 2H), 1.81-1.77 (m, 2H), 1.17 (t, J = 7.5Hz, 3H).

M^-(ES): 301.2; M^+(ES): 303.3; HPLC (max plot) 67.8% ; Rt: 1.41 min.

Example 39: (2-{[2-(6-aminopyridin-3-yl)ethyl]amino}pyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and (tert-butoxy)-N-))5-aminoethyl)(2-pyridyl))carboxamide in the presence of triethylamine for overnight at 70°C in EtOH (75.4%).

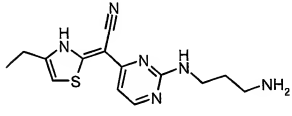
M^+(ES): 466.0; HPLC (max plot) 87.7%; Rt: 2.30 min.

The Boc protected intermediate tert-butyl 5-[2-({4-[cyano(4-ethyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)ethyl]pyridin-2-ylcarbamate was treated with a solution of 20% TFA in DCM overnight at rt, affording the title compound as a diTFA salt after evaporation of the solvent (yellow powder, 61.1%).

^{1}H NMR (DMSO-d_6) δ 8.03-7.91 (m, 3H), 7.89-7.85 (m, 1H), 7.80 (br d, 1H), 7.64-7.54 (m, 1H), 6.95-6.92 (m, 2H), 6.38 (d, J = 7.2Hz, 1H), 3.82-3.68 (m, 2H), 2.85-2.81 (m, 2H), 2.68 (q, J = 7.5Hz, 2H), 1.20 (t, J = 7.5Hz, 3H).

M^+(ES): 366.2; HPLC (max plot) 100% ; Rt: 1.75 min.

Example 40: {2-[(3-aminopropyl)amino]pyrimidin-4-yl}(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

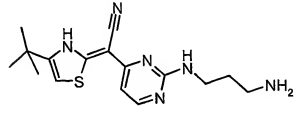


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1,3-diaminopropane in the presence of triethylamine for 4 min at 155°C in EtOH (67%).

^{1}H NMR (DMSO-d_6) δ 7.47 (br d, 1H), 6.41 (s, 1H), 6.11 (br d, 1H), 3.52-3.39 (m, 2H), 2.82-2.77 (m, 2H), 2.56 (q, J = 7.5Hz, 2H), 1.83-1.72 (m, 2H), 1.17 (t, J = 7.5Hz, 3H).

HPLC (max plot) 77.2% ; Rt: 1.43 min.

Example 41: {2-[(3-aminopropyl)amino]pyrimidin-4-yl}(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

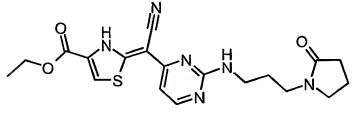


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-chloropyrimidin-4-yl)acetonitrile and 1,3-diaminopropane in the presence of triethylamine for 2 min at 155°C in EtOH (73.1%).

^{1}H NMR (DMSO-d_6) δ 7.50-7.35 (m, 2H, 1exchangeable), 6.40 (s, 1H), 6.11 (d, J = 6 Hz, 1H), 3.80-3.20 (m, 2H), 2.95-2.65 (m, 2H), 1.95-1.65 (m, 2H), 1.24 (s, 9H).

M$^-$(ES): 329; M$^+$(ES): 331; HPLC (max plot) 78% ; Rt: 1.79 min.

Example 42: ethyl-2-[cyano(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)methylene]-2,3-dihydro-1,3-thiazole-4-carboxylate

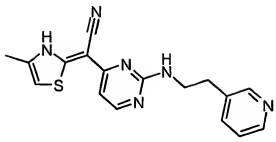


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from ethyl-2-[(2-chloropyrimidin-4-yl)(cyano)methylene]-2,3-dihydro-1,3-thiazole-4-carboxylate and N-(3'-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 10 min at 155°C in EtOH as a yellow fluffy solid (51.4%).

^{1}H NMR (DMSO-d_6) δ 10.82 (s, 1H), 8.06 (s, 1H), 7.43 (s, 1H), 7.37 (d, J = 6.8Hz, 1H), 6.27 (d, J = 5.5Hz, 1H), 4.28 (q, J = 7.2Hz, 2H), 3.48 (m, 2H), 3.32 (t, J = 7.2Hz, 2H), 3.27 (t, J = 7.2Hz, 2H), 2.19 (t, J = 7.9Hz, 2H), 1.88 (quint, J = 7.1Hz, 2H), 1.79 (quint, J = 6.8Hz, 2H), 1.29 (t, J = 7.1Hz, 3H).

M$^-$(ES): 413; M$^+$(ES): 415; HPLC (max plot) 99.2% ; Rt: 2.47 min.

Example 43: (4-methyl-1,3-thiazol-2(3H)-ylidene){2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

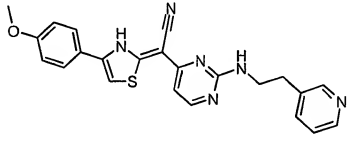


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine for 33 min at 155°C in mixture of iPrOH/EtOH as a light yellow powder (66.1%).

^{1}H NMR (DMSO-d_6) δ 8.66 (d, J=1.5 Hz, 1H); 8.61 (dd, J=1.5Hz, J=5.3Hz, 1H); 8.07 (d, J=7.9Hz, 1H); 7.66 (m, 2H), 7.01(s, 1H); 6.45 (d, J=7.2Hz, 1H); 3.86 (s, 2H); 3.07 (t, J=6.4Hz, 2H); 2.33 (d, J=0.8Hz, 3H)

M^-(ES): 335; M^+(ES): 337; HPLC (max plot) 80% ; Rt: 1.35 min.

Example 44 : [4-(4-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

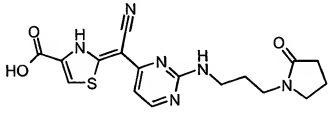


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)[4-(4-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine for 33 min at 155°C in EtOH as a dark yellow powder (47.8%).

^{1}H NMR (DMSO-d_6) δ 10.73 (br s, 1H); 8.76 (s, 1H); 8.70 (d, J=4.5 Hz, 1H); 8.26 (d, J=8.3Hz, 1H); 7.88 (d, J=8.6Hz, 2H); 7.82 (dd, J=7.9 Hz, J= 5.3 Hz, 1 H); 7.53 (d, J=7.2Hz, 1H); 7.49 (s,1H); 7.34 (d, J=7.5Hz 1H);6.98 (d, J=9.1 Hz, 2H); 6.28 (d, J= 7.2 Hz, 1H); 3.90(d, J= 5.6Hz, 2H); 3.79 (s, 3H); 3.13 (t, J=6.8 Hz, 2H)

M^-(ES): 427; M^+(ES): 429; HPLC (max plot) 94.5% ; Rt: 2.14 min.

Example 45: 2-[cyano(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)methylene]-2,3-dihydro-1,3-thiazole-4-carboxylic acid

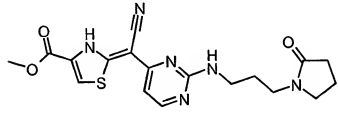


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from ethyl 2-[(2-chloropyrimidin-4-yl)(cyano)methylene]-2,3-dihydro-1,3-thiazole-4-carboxylate and N-(3'-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 70 h at 70°C in EtOH as a yellow powder (61.5%).

^{1}H NMR (DMSO-d_6) δ 12.65 (br s, 1H); 10.80 (s, 1H); 8.01 (s, 1H); 7.36 (d, 1H, *J*=7.2Hz); 7.36 (br s, 1H); 6.27 (d, *J*=7.1Hz; 1H); 3.38 (m, 6H); 2.20 (t, *J*=7.6Hz, 2H); 2.08 (quint, *J*=7.5 Hz, 2H); 1.99 (quint, *J*=6.8 Hz, 2H)

M^-(ES): 341; M^+(ES): 387; HPLC (max plot) 93% ; Rt: 1.82 min.

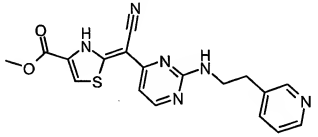
Example 46: methyl-2-[cyano(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)methylene]-2,3-dihydro-1,3-thiazole-4-carboxylate



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from methyl 2-[(2-chloropyrimidin-4-yl)(cyano)methylene]-2,3-dihydro-1,3-thiazole-4-carboxylate and N-(3'-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 10 min at 145°C in MeOH as a yellow powder (68.9%).

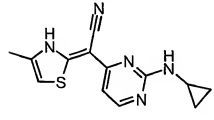
^{1}H NMR (DMSO-d_6) δ 10.78 (s, 1H); 8.04 (s, 1H); 7.38 (s, 1H); 7.32 (d, *J*=6.8Hz, 1H); 6.22 (d, *J*=7.1Hz, 1H); 3.75 (s, 3H); 3.43 (d, *J*=4.9Hz, 2H); 3.28 (t, *J*=6.8Hz, 2H); 3.22 (t, *J*=7.2Hz, 2H); 2.14 (t, *J*=7.9Hz, 2H); 1.84 (m, 2H); 1.75 (m, 2H)
M^-(ES): 399; M^+(ES): 401; HPLC (max plot) 99% ; Rt: 2.24 min.

Example 47: methyl-2-(cyano{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}methylene)-2,3-dihydro-1,3-thiazole-4-carboxylate



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from methyl-2-[(2-chloropyrimidin-4-yl)(cyano)methylene]-2,3-dihydro-1,3-thiazole-4-carboxylate and 3-(2-aminoethyl)pyridine in the presence of triethylamine for 10 min at 145°C in MeOH as a yellow powder (54.3%).
^{1}H NMR (DMSO-d_6) δ 10.82 (s,1H); 8.71 (s,1H); 8.66 (d, *J*=4.9Hz,1H); 8.18 (d, *J*=7.9Hz,1H); 8.08 (s,1H); 7.75 (dd, *J*=7.5Hz, *J*=5.2Hz,1H); 7.57 (br s, 1H); 7.38 (d, *J*=7.2Hz,1H); 6.29 (d, *J*=7.1Hz; 1H); 3.86 (m, 2H); 3.81(s, 3H); 3.08 (t, *J*=6.8Hz, 2H)
M^-(ES): 379; M^+(ES): 381; HPLC (max plot) 97% ; Rt: 1.63 min.

Example 48: [2-(cyclopropylamino)pyrimidin-4-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



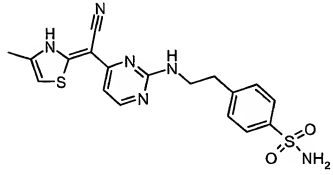
Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-

ylidene)acetonitrile and cyclopropyl amine in the presence of triethylamine for 10 min at 155°C in EtOH as a yellow powder (73.1%).

^{1}H NMR (Acetone-d_6) δ 14 (br s, 1H); 10.15 (s,1H); 7.79 (d, *J*=7.2Hz,1H); 7.04 (s, 1H); 6.56 (d, *J*=6.8Hz,1H); 3.05 (br s,1H); 2.47 (s, 3H); 0.99 (d, *J*=5.2Hz, 2H); 0.77(s, 2H).

M^-(ES): 270; M^+(ES): 272; HPLC (max plot) 95% ; Rt: 2.00 min.

Example 49: 4-[2-({4-[cyano(4-methyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)ethyl]benzenesulfonamide

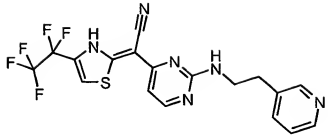


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 4-(2-aminoethyl)benzenesulfonamide in the presence of triethylamine for 10 min at 155°C in EtOH as a yellow powder (69.4%).

^{1}H NMR (DMSO-d_6) δ 7.90 (br s, 1H); 7.77 (d, *J*= 8.3Hz, 2H); 7.67 (d, *J*= 6.4Hz, 1H); 7.47 (d, *J*= 7.9Hz, 2H); 7.31 (s, 2H); 7.02 (s, 1H); 6.46 (d, *J*= 6.8Hz, 1H); 3.84 (s, 2H); 3.03 (t, *J*= 6.8Hz, 2H); 2.33 (d, *J*= 0.7Hz, 3H)

M^-(ES): 415; M^+(ES): 413; HPLC (max plot) 92% ; Rt: 2.13 min.

Example 50: [4-(pentafluoroethyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

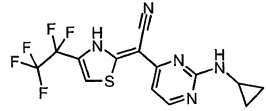


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)[4-(pentafluoroethyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine for 3 min at 155°C in EtOH as a yellow powder (56.1%).

^{1}H NMR (DMSO-d_6) δ 10.96 (s, 1H); 8.72 (d, *J*=1.5Hz, 1H); 8.67 (dd, *J*=4.2Hz, *J*= 1.1Hz, 1H); 8.20 (d, *J*=8.3Hz, 1H); 7.97 (s, 1H); 7.76 (dd, *J*= 5.3Hz, *J*=7.9Hz, 1H); 7.67 (br s, 1H); 7.42 (m, 1H); 6.32 (d, *J*=7.2Hz, 1H); 3.86 (s, 2H); 3.09 (t, *J*=6.8Hz, 2H)

M^+(ES): 441.1; HPLC (max plot) 99.4% ; Rt: 2.90 min.

Example 51: [2-(cyclopropylamino)pyrimidin-4-yl][4-(pentafluoroethyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile

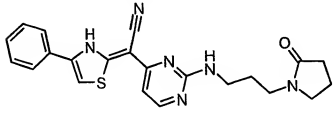


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)[4-(pentafluoroethyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile and cyclopropyl amine in the presence of triethylamine for 3 min at 155°C in EtOH as a yellow powder (95.3%).

^{1}H NMR (DMSO-d_6) δ 10.81 (s, 1H), 7.95 (s, 1H), 7.40 (d, *J* = 7.2Hz, 1H), 6.34 (d, *J*= 7.1Hz, 1H), 2.81 (br s, 1H), 0.85 (m, 2H), 0.62 (m, 2H).

M^-(ES): 374; M^+(ES): 376; HPLC (max plot) 99.9% ; Rt: 3.88 min.

Example 52: (2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

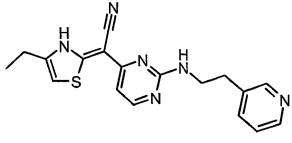


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and N-(3'-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 4.5 d at 70°C in EtOH as a yellow powder (86%).

^{1}H NMR (DMSO-d_6) δ 7.88 (d, J = 7.1 Hz, 2H), 7.62 (s, 1H), 7.38-7.24 (m, 5H), 6.23 (d, J = 7.1Hz, 1H), 3.51-3.41 (m, 2H), 3.31-3.21 (m, 4H), 2.18-2.12 (m, 2H), 1.86-1.74 (m, 4H).

M^+(ES): 419.3; HPLC (max plot) 97% ; Rt: 2.63 min.

Example 53: (4-ethyl-1,3-thiazol-2(3H)-ylidene){2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

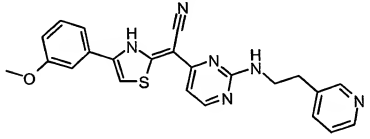


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine for overnight at 70°C in EtOH as a beige powder (71%).

^{1}H NMR (DMSO-d_6) δ 8.68 (d, J = 1.5Hz, 1H), 8.62 (dd, J = 5Hz, J = 1.5Hz, 2H), 8.10 (br d, 1H), 7.69-7.65 (m, 2H), 6.99 (s, 1H), 6.43 (d, J = 7.2Hz, 1H), 3.93-3.80 (m, 2H), 3.09-3.05 (m, 2H), 2.73-2.66 (m, 2H), 1.20 (t, J = 7.5Hz, 3H).

M^+(ES): 351.3; HPLC (max plot) 97% ; Rt: 1.58 min.

Example 54: [4-(3-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

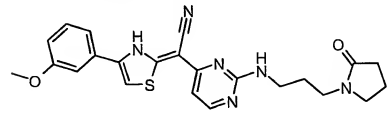


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)[4-(3-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine for 5 min at 165°C in EtOH as a yellow powder (46%).

^{1}H NMR (DMSO-d_6) δ 8.78 (d, J = 1.5Hz, 1H), 8.73-8.71 (m, 1H),8.32 (br d, 1H), 7.88-7.84 (m, 1H), 7.67 (s, 1H), 7.54-7.49 (m, 3H), 7.36-7.30 (m, 2H), 6.90-6.87 (m, 1H), 6.28 (d, J = 7.2Hz, 1H), 3.91-3.80 (m, 2H), 3.80 (s, 3H), 3.13 (t, J = 6.8Hz, 2H).

M^+(ES): 429.2; HPLC (max plot) 99% ; Rt: 2.19 min.

Example 55: [4-(3-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene](2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

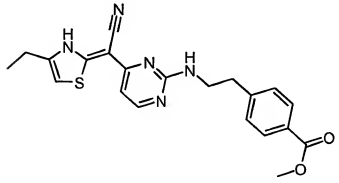


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)[4-(3-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile and N-(3'-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 5 min at 165°C in EtOH as a green powder (88%).

^{1}H NMR (DMSO-d_6) δ 10.86 (br s, 1H), 7.69 (s, 1H), 7.53-7.49 (m, 2H), 7.37-7.30 (m, 3H), 6.69-6.87 (m, 1H), 6.28 (d, J = 7.1Hz, 1H), 3.80 (s, 3H), 3.52-3.51 (m, 2H), 3.36-3.26 (m, 4H), 2.24-2.18 (m, 2H), 1.92-1.79 (m, 4H).

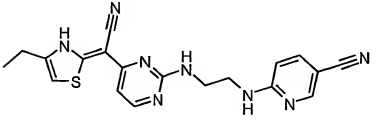
M^+(ES): 449.3; HPLC (max plot) 96% ; Rt: 2.79 min.

Example 56: methyl 4-[2-({4-[cyano(4-ethyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)ethyl]benzoate



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and HCl salt of methyl-4-(2-aminoethyl)benzoate in the presence of triethylamine for 5 min at 155°C in EtOH as a yellow powder (41.4%).
^{1}H NMR (DMSO-d_6) δ 7.92 (d, J = 8.3Hz, 2H), 7.93-7.90 (br s, 1H), 7.62 (br d, 1H), 7.43 (d, J = 8.3Hz, 2H), 6.42 (d, J = 7.2Hz, 1H), 3.90-3.78 (m, 2H), 3.83 (s, 3H), 3.02 (br t, 2H), 2.68 (q, J = 7.5Hz, 2H), 1.20 (t, J = 7.5Hz, 3H).
M^+(ES): 408.1; HPLC (max plot) 99.2% ; Rt: 2.97 min.

Example 57: 6-{[2-({4-[-cyano(4-ethyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)ethyl]amino}nicotinonitrile



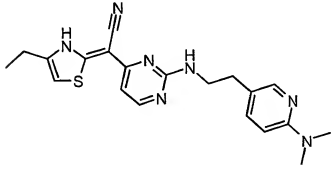
Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-

ylidene)acetonitrile and 6-[(2-aminoethyl)amino]pyridine-3-carbonitrile in the presence of triethylamine for 5 min at 155°C in EtOH as a yellow powder (68.7%).

^{1}H NMR (DMSO-d_6) δ 8.37 (d, J = 1.8Hz, 1H), 8.05 (br s, 1H), 7.75-7.63 (m, 3H), 6.97 (s, 1H), 6.53 (d, J = 9Hz, 1H), 6.45 (d, J = 7.1Hz, 1H), 3.71-3.55 (m, 4H), 2.69 (q, J = 7.5Hz, 2H), 1.21 (t, J = 7.5Hz, 3H).

M^+(ES): 391.3; HPLC (max plot) 99.3% ; Rt: 2.24 min.

Example 58: [2-({2-[6-(dimethylamino)pyridin-3-yl]ethyl}amino)pyrimidin-4-yl](4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

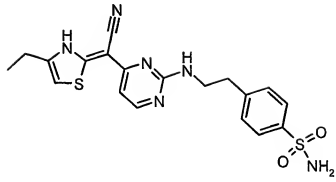


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 2-(N,N-dimethylamino)-5-aminoethyl pyridine in the presence of triethylamine for 5 min at 155°C in EtOH as a yellow powder (97.4%).

^{1}H NMR (DMSO-d_6) δ 8.07 (brs, 1H), 7.91-7.88 (m, 2H), 7.84 (s, 1H), 7.64 (br d, 1H), 6.15 (d, J = 9Hz, 2H), 7.00 (s, 1H), 6.42 (d, J = 7.2Hz, 1H), 3.78 (br t, 2H), 3.15 (s, 6H), 2.88 (t, J = 6.4Hz, 2H), 2.70 (q, J = 7.5Hz, 2H), 1.21 (t, J = 7.5Hz, 3H).

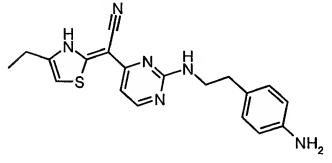
M^+(ES): 394.3; HPLC (max plot) 99.9% ; Rt: 1.76 min.

Example 59: 4-[2-({4-[cyano(4-ethyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)ethyl]benzenesulfonamide



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 4-(2-aminoethyl)benzenesulfonamide in the presence of triethylamine for 5 min at 155°C in EtOH as a yellow powder (85.7%).
^{1}H NMR (DMSO-d_6) δ 7.88 (brs, 1H), 7.76 8d, J = 8.2Hz, 2H), 7.62 (br d, 1H), 7.46 (d, J = 8.2Hz, 2H), 7.29 (s, 2H), 7.00 (s, 1H), 6.41 (d, J = 7.1Hz, 1H), 4.00-3.70 (m, 2H), 3.02 (t, J = 6.8Hz, 2H), 2.69 (q, J = 7.5Hz, 2H), 1.21 (t, J = 7.5Hz, 3H).
M^+(ES): 429.3; HPLC (max plot) 99.7% ; Rt: 2.28 min.

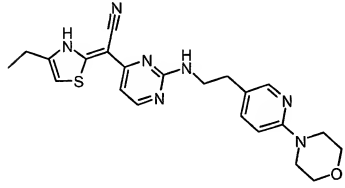
Example 60: (2-{[2-(4-aminophenyl)ethyl]amino}pyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 4-(tert-butoxycarbonylamino)phenylethylamine in the presence of triethylamine for 5 min at 155°C in EtOH. The Boc protected intermediate was treated with a solution of 20% TFA in DCM overnight at rt, affording the title compound as a diTFA salt after evaporation of the solvent (yellow powder, 87.4%).

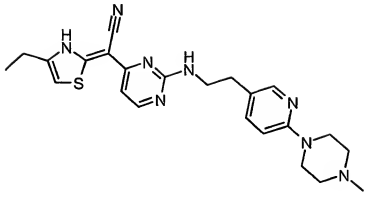
^{1}H NMR (DMSO-d_6) δ 8.12 (br s, 1H), 7.68 (br d, 1H), 7.30 (d, J = 8.3Hz, 2H), 7.14 (d, J = 8.3Hz, 2H), 7.01 (s, 1H), 6.45 (d, J = 7.2Hz, 1H), 3.85-3.72 (m, 2H), 2.93 (br t, 2H), 2.69 (q, J = 7.5Hz, 2H), 1.20 (t, J = 7.5Hz, 3H).
M^+(ES): 365.2; HPLC (max plot) 98% ; Rt: 1.76 min.

Example 61: (4-ethyl-1,3-thiazol-2(3H)-ylidene)(2-{[2-(6-morpholin-4-ylpyridin-3-yl)ethyl]amino}pyrimidin-4-yl)acetonitrile



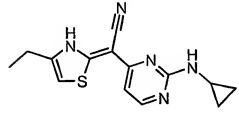
Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 2-[6-morpholin-4-yl-pyridin-3-yl]ethanamine in the presence of triethylamine for 5 min at 155°C in EtOH as a yellow powder (97.6%).
^{1}H NMR (DMSO-d_6) δ 8.05 (br s, 1H), 7.97 (d, J = 1.9Hz, 1H), 7.72-7.69 (m, 2H), 7.04-7.02 (m, 2H), 6.47 (d, J = 7.1Hz, 1H), 3.77 (br t, 2H), 3.71 (t, J = 4.9Hz, 4H), 3.46 (t, J = 4.9Hz, 4H), 2.86 (t, J = 6.4Hz, 2H), 2.71 (q, J =7.5Hz, 2H), 1.21 (t, J = 7.5Hz, 3H).
M^+(ES): 436.3; HPLC (max plot) 98.5% ; Rt: 1.74 min.

Example 62: (4-ethyl-1,3-thiazol-2(3H)-ylidene)[2-({2-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]ethyl}amino)pyrimidin-4-yl]acetonitrile



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 2-[6-(4-methylpiperazin-1-yl-pyridin-3-yl]ethanamine in the presence of triethylamine for 5 min at 155°C in EtOH as a yellow powder (29.3%).
^{1}H NMR (DMSO-d_6) δ 8.06 (d, J = 2.3Hz, 1H), 7.93 (br s, 1H), 7.61 (br d, 1H), 7.57 (dd, J = 2.3Hz, J = 8.7Hz, 1H), 6.97(s, 1H), 6.93 (d, J = 8.7Hz, 1H), 6.41 (d, J =6.8Hz, 1H), 4.35-4.32 (m, 2H), 3.82-3.68 (m, 2H), 3.51-3.48 (m, 2H), 3.06-3.03 (m, 4H), 2.84 (s, 3H), 2.84-2.81 (m, 2H), 2.69 (q, J = 7.5Hz, 2H), 1.20 (t, J = 7.5Hz, 3H).
M^+(ES): 449.1; HPLC (max plot) 87.8% ; Rt: 1.52 min.

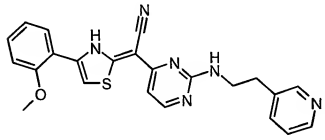
Example 63: [2-(cyclopropylamino)pyrimidin-4-yl](4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclopropyl amine in the presence of triethylamine for 5 min at 155°C in EtOH as a yellow powder (78.6%).

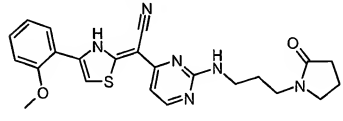
^{1}H NMR (DMSO-d_6) δ 8.63 (br s, 1H), 7.71 (d, J = 6.8Hz, 1H), 7.04 (s, 1H), 6.48 (d, J = 6.8Hz, 1H), 2.91-2.77 (m, 1H), 2.69 (q, J = 7.6Hz, 2H), 1.20 (t, J = 7.6Hz, 3H), 0.93-0.86 (m, 2H), 0.68-0.62 (m, 2H).
M^+(ES): 286.3; HPLC (max plot) 97.5% ; Rt: 1.66 min.

Example 64: [4-(2-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)[4-(2-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine for 5 min at 155°C in EtOH as a yellow powder (28.4%).
^{1}H NMR (DMSO-d_6) δ 8.74 (br d, 1H), 8.68-8.67 (m, 1H), 8.23-8.17 (m, 2H), 7.80-7.75 (m, 1H), 7.70 (s, 1H), 7.51 (br t, 1H), 7.35-7.27 (m, 2H), 7.12-7.01 (m, 2H), 6.28 (d, J = 7.6Hz, 1H), 3.91 (s, 3H), 3.91-3.85 (m, 2H), 3.13-3.09 (m, 2H).
M^+(ES): 429.1; HPLC (max plot) 98.3% ; Rt: 2.20 min.

Example 65: [4-(2-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene](2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile



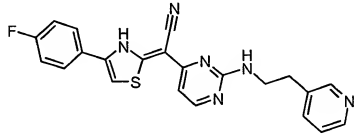
Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)[4-(2-methoxyphenyl)-1,3-thiazol-

2(3H)-ylidene]acetonitrile and N-(3'-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 5 min at 155°C in EtOH as a yellow powder (71.9%).

^{1}H NMR (DMSO-d_6) δ 8.07 (br d, 1H), 7.70 (s, 1H), 7.53 (br t, 1H), 7.43 (d, J = 7.2 Hz, 1H), 7.36-7.30 (m, 1H), 7.12 (d, J = 8Hz, 1H), 7.05 (dt, J = 0.8Hz, J = 7.5Hz, 1H), 6.32 (d, J = 7.2Hz, 1H), 3.90 (s, 3H), 3.52-3.51 (m, 2H), 3.36-3.27 (m, 4H), 2.23-2.18 (m, 2H), 1.92-1.79 (m, 4H).

M^+(ES): 449.2; HPLC (max plot) 99.1% ; Rt: 2.85 min.

Example 66: [4-(4-fluorophenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

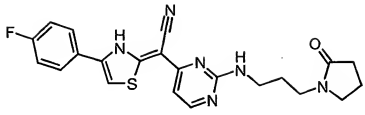


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)[4-(4-fluorophenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine for 4 min at 155°C in EtOH as a yellow powder (60.3%).

^{1}H NMR (DMSO-d_6) δ 10.79 (br s, 1H), 8.79 (d, J = 1.5Hz, 1H), 8.74-8.72 (m, 1H), 8.34-8.31 (m, 1H), 8.01-7.96 (m, 2H), 7.89-7.84 (m, 1H), 7.63 (s, 1H), 7.56 (br t, 1H), 7.34 (d, J = 7.1Hz, 1H), 7.28-7.22 (m, 2H), 6.28 (d, J = 7.1Hz, 1H), 3.91-3.89 (m, 2H), 3.16-3.11 (m, 2H).

M^+(ES): 416.8; HPLC (max plot) 99.9% ; Rt: 2.16 min.

Example 67: [4-(4-fluorophenyl)-1,3-thiazol-2(3H)-ylidene](2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

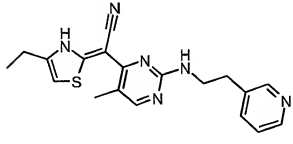


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)[4-(4-fluorophenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile and N-(3'-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 4 min at 155°C in EtOH as a yellow powder (95.3%).

^{1}H NMR (DMSO-d_6) δ 10.77 (br s, 1H), 8.00-7.95 (m, 2H), 7.65 (s, 1H), 7.39 (br t, 1H), 7.35 (d, J = 7.5Hz, 1H), 7.27-7.21 (m, 2H), 6.28 (d, J = 7.5Hz, 1H), 3.52-3.50 (m, 2H), 3.36-3.26 (m, 4H), 2.24-2.18 (m, 2H), 1.92-1.79 (m, 4H).

M^+(ES): 437.2; HPLC (max plot) 98.2% ; Rt: 2.77 min.

Example 68: (4-ethyl-1,3-thiazol-2(3H)-ylidene){5-methyl-2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

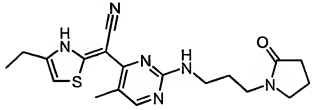


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine for 16 min at 155°C in EtOH as a yellow powder (82.5%).

^{1}H NMR (DMSO-d_6) δ 8.70 (d, J = 1.5Hz, 1H), 8.65-8.64 (m, 1H), 8.16-8.13 (m, 1H), 8.04 (br t, 1H), 7.73-7.69 (m, 1H), 7.56 (s, 1H), 7.03 (s, 1H), 3.88-3.75 (m, 2H), 3.08-3.04 (m, 2H), 2.71 (q, J = 7.6Hz, 2H), 2.33 (s, 3H), 1.19 (t, J = 7.6Hz, 3H).

M^+(ES): 365.2; HPLC (max plot) 97.5% ; Rt: 1.74 min.

Example 69: (4-ethyl-1,3-thiazol-2(3H)-ylidene)(5-methyl-2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

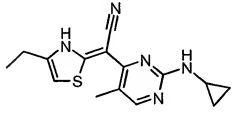


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and N-(3'-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 2x4 min at 155°C in EtOH as a yellow powder (86.2%).

^{1}H NMR (DMSO-d_6) δ 8.04 (br t, 1H), 7.59 (s, 1H), 7.08 (s, 1H), 3.52-3.39 (m, 2H), 3.35-3.26 (m, 4H), 2.74 (q, J = 7.5Hz, 2H), 2.33 (s, 3H), 2.19 (t, J = 7.9Hz, 2H), 1.92-1.77 (m, 4H), 1.20 (t, J = 7.5Hz, 3H).

M^+(ES): 385.3; HPLC (max plot) 97.8% ; Rt: 2.37 min.

Example 70: [2-(cyclopropylamino)-5-methylpyrimidin-4-yl](4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

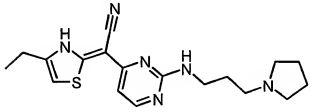


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclopropyl amine in the presence of triethylamine for 4 min at 155°C in EtOH as a yellow powder (77%).

^{1}H NMR (DMSO-d_6) δ 8.55 (br t, 1H), 7.57 (s, 1H), 7.07 (s, 1H), 2.82-2.67 (m, 3H), 2.34 (s, 3H), 1.20 (t, J = 7.5Hz, 3H), 0.89-0.86 (m, 2H), 0.65-0.63 (m, 2H).

M^+(ES): 300.2; HPLC (max plot) 97.8% ; Rt: 2.44 min.

Example 71: (4-ethyl-1,3-thiazol-2(3H)-ylidene){2-[(3-pyrrolidin-1-ylpropyl)amino]pyrimidin-4-yl}acetonitrile

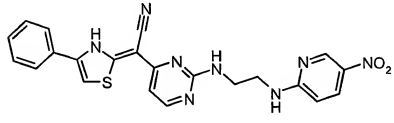


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1-(3-aminopropyl)pyrrolidine in the presence of triethylamine for 4 min at 155°C in EtOH as a yellow powder (46.4%).

^{1}H NMR (DMSO-d_6) δ 9.60 (br s, 1H), 8.09 (br s, 1H), 7.62 (br d, 1H), 6.98 (s, 1H), 6.41 (d, J = 6.7Hz, 1H), 3.64-3.45 (m, 4H), 3.24-3.18 (m, 2H), 3.06-2.88 (m, 2H), 2.69 (q, J = 7.5Hz, 2H), 2.06-1.74 (m, 6H), 1.21 (t, J = 7.5Hz, 3H).

M^+(ES): 357.2; HPLC (max plot) 99.9% ; Rt: 1.58 min.

Example 72: [2-({2-[(5-nitropyridin-2-yl)amino]ethyl}amino)pyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

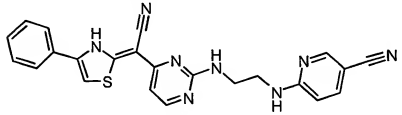


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 2-(2-aminoethylamino)-5-nitro-pyridine in the presence of triethylamine for 24 h at 70°C in EtOH as a green powder (26%).

^{1}H NMR (DMSO-d_6) δ 11.80-11.70 (br s, 1H exchangeable), 8.92 (d, J = 2.7, 1H), 8.35-8.27 (br s, 1H exchangeable), 8.15-8.05 (m, 1H), 7.96-7.88 (m, 2H), 7.62 (s, 1H), 7.58-7.51

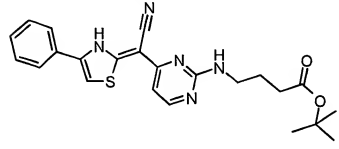
(br s, 1H exchangeable),7.46-7.24 (m, 4H [3+1]), 6.59 (d, J = 9.4 Hz, 1H), 6.30 (d, J = 7.2 Hz, 1H), 4.70-3.85 (br s, 2 H exchangeable), 3.80-3.60 (m, 4H).
M^+(ES): 459.4; HPLC (max plot) 91% ; Rt: 3.05min.

Example 73: 6-{[2-({4-[cyano(4-phenyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)ethyl]amino}nicotinonitrile



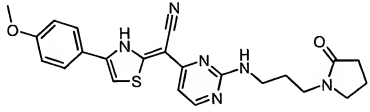
Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 2-(2-aminoethylamino)-5-cyano-pyridine in the presence of triethylamine for overnight at 70°C in EtOH as a yellow powder (54%).
^{1}H NMR (DMSO-d_6) δ 11.85-11.75 (br s, 1H exchangeable), 8.41(d, J = 2.2, 1H), 7.96-7.88 (m, 2H), 7.85-7.75 (br s, 1H exchangeable), 7.72-7.61(m, 2H), 7.60-7.50 (br s, 1H exchangeable), 7.46-7.24 (m, 4H [3+1]), 6.57 (d, J = 9.0 Hz, 1H), 6.30 (d, J = 7.2 Hz, 1H), 5.50-4.20 (br s, 2 H exchangeable), 3.80-3.60 (m, 4H).
M^+(ES): 439.2 HPLC (max plot) 98% ; Rt: 2.78 min.

Example 74: tert-butyl 4-({4-[cyano(4-phenyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)butanoate



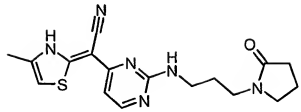
Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 4-amino-N-butyric acid tert-butyl ester hydrochloride in the presence of triethylamine for 36 h at 70°C in EtOH as a yellow powder (49.6%).
^{1}H NMR (DMSO-d_6) δ 10.8-10.4 (br s, 1H exchangeable), 7.98-7.90 (m, 2H), 7.68 (s, 1H), 7.53-7.48 (br s, 1H exchangeable), 7.46-7.24 (m, 5H [3+1+1]), 6.29 (d, J= 7.2 Hz, 1H), 5.40-4.10 (br s, 1H exchangeable), 3.65-3.45 (br s, 2H), 2.32 (t, J= 7.5 Hz, 2H), 1.85 (q, J = 7.1 Hz, 2H), 1.38 (s, 9H).
M^-(ES): 434.3; M^+(ES): 436.3; HPLC (max plot) 99% ; Rt: 3.54 min.

Example 75: [4-(4-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene](2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)[4-(4-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile and 1-(3-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for overnight at 70°C in EtOH as a yellow powder (16.7%).
^{1}H NMR (DMSO-d_6) δ 11.0-10.65 (br s, 1H exchangeable), 7.86 (d, J = 8.6 Hz, 2H), 7.51 (s, 1H), 7.55-7.45 (m, 2H [1+1 exchangeable]), 6.98 (d, J = 9.1 Hz, 2H), 6.27 (d, J = 7.2 Hz, 1H), 4.24-3.62 (m, 4H [3+1exchangeable]), 3.58-3.45 (m, 2H), 3.40-3.22 (m, 2H), 2.25-2.15 (t, J = 7.9 Hz, 2H), 1.98-1.79 (m, 4H).
M^-(ES): 447.3; M^+(ES): 449.3; HPLC (max plot) 98% ; Rt: 2.76 min.

Example 76: (4-methyl-1,3-thiazol-2(3H)-ylidene)(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

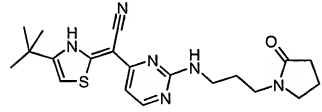


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1-(3-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 5 min at 155°C in EtOH as a yellow powder (50.4%).

^{1}H NMR (DMSO-d_6) δ 8.10-7-95 (br s, 1H,exchangeable), 7.69 (d, J = 7.2 Hz, 1H), 7.03 (s, 1H), 6.44 (d, J = 7.1 Hz, 1 H), 4.50- 3.40 (br s, 1H + H2O), 3.60-3.45 (m, 2H), 3.38-3.20 (m, 4H), 2.33 (d, J = 0.7 Hz, 3H), 2.30-2.10 (m, 2H), 2.00-1.75 (m, 4H [2+2]).

HPLC (max plot) 96.7% ; Rt: 1.97 min.

Example 77: (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

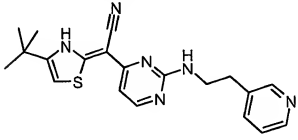


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-chloropyrimidin-4-yl)acetonitrile and 1-(3-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 4 min at 155°C in iPrOH as a yellow powder (49.5%).

^{1}H NMR (DMSO-d_6) δ 11.06 (br s, 1H, exchangeable), 7.80-7.10 (m, 2H, including 1 exchangeable), 6.82 (s, 1H), 6.26 (d, J = 7.2Hz), 4.70-3.45 (br s, 1H, exchangeable), 3.50-3.10 (m, 6H [2+4]), 2.15 (t, J = 7.9 Hz, 2H), 1.90-1.65 (m, 4H), 1.22 (s, 9H).

M^-(ES): 397; M^+(ES): 399; HPLC (max plot) 99% ; Rt: 2.60 min.

Example 78: (4-tert-butyl-1,3-thiazol-2(3H)-ylidene){2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

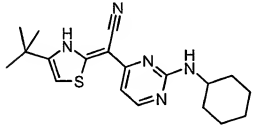


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-chloropyrimidin-4-yl)acetonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine for 5 min at 165°C in iPrOH as a yellow powder (72.7%).

^{1}H NMR (DMSO-d_6) δ 8.80-8.65 (m, 2H),8.71 (d, J = 7.9 Hz, 1H), 7.90-7.65 (m, 2H, including 1 exchangeable), 7.42 (d, J = 7.2 Hz, 1H), 6.84 (s, 1H), 6.32 (d, J = 7.2 Hz, 1H), 3.95-3.80 (m, 2H), 3.15-3.05 (m, 2H), 1.28 (m, 9H).

M^-(ES): 377; M^+(ES): 379; HPLC (max plot) 98% ; Rt: 1.90 min.

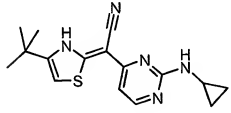
Example 79: (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)[2-(cyclohexylamino)pyrimidin-4-yl]acetonitrile



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-chloropyrimidin-4-yl)acetonitrile and cyclohexyl amine in the presence of triethylamine for 5 min at 165°C in iPrOH as a bright yellow powder (54.9%).

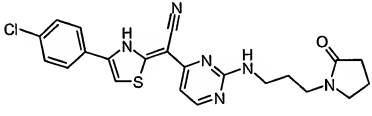
^{1}H NMR (DMSO-d_6) δ 10.61 (br s, 1H, exchangeable), 7.75-7.35 (m, 2H, including 1 exchangeable), 6.97 (s, 1H), 6.32 (d, J = 6.8 Hz, 1H), 4.10-3.95 (m, 1H), 2.10-1.85 (m, 2H), 1.80-1.50 (m, 2H), 1.48-1.10 (m, 14H, [9+5]).
M^-(ES): 354; M^+(ES): 356; HPLC (max plot) 99.9% ; Rt: 3.34 min.

Example 80: (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)[2-(cyclopropylamino)pyrimidin-4-yl]acetonitrile



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-chloropyrimidin-4-yl)acetonitrile and cyclopropyl amine in the presence of triethylamine for 3 min at 155°C in EtOH as a yellowish powder (78.6%).
^{1}H NMR (DMSO-d_6) δ 11.0 (br s, 1H, exchangeable), 8.26 (br s, 1H, exchangeable), 7.52 (s, 1H), 6.93 (s, 1H), 6.42 (d, J = 6.8 Hz [from D2O spectrum], 1H), 3.00-2.75 (m, 1H), 1.29 (s, 9H), 0.95-0.78 (m, 2H), 0.72-0.52 (m, 2H).
M^-(ES): 312; M^+(ES): 314; HPLC (max plot) 98.5% ; Rt: 2.68 min.

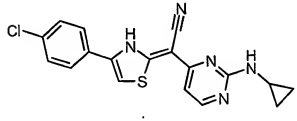
Example 81: [4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from [4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-

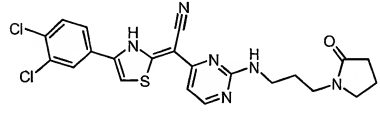
chloropyrimidin-4-yl)acetonitrile and 1-(3-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 5 min at 155°C in EtOH as a yellow powder (96.4%).
^{1}H NMR (DMSO-d_6) δ 10.83 (br s, 1H), 7.98 (d, J = 8.29Hz, 2H,), 7.74 (s, 1H), 7.49 (d, J = 8.29Hz, 2H), 7.4 (s, 1H), 7.37 (d, J = 7.53Hz, 1H), 6.29 (d, J = 7.54Hz, 1H), 3.48-3.52 (m, 2H), 3.26-3.36 (m, 4H), 2.21 (t, J = 7.91Hz, 2H), 1.79-192 (m, 4H)
HPLC (max plot) 99.9% ; Rt: 3.03 min.

Example 82: [4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene][2-(cyclopropylamino)pyrimidin-4-yl]acetonitrile



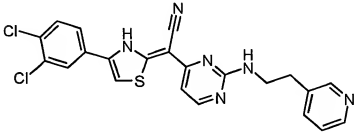
Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from [4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-chloropyrimidin-4-yl)acetonitrile and cyclopropyl amine in the presence of triethylamine for 5 min at 155°C in EtOH as a yellow powder (62.3%).
^{1}H NMR (DMSO-d_6) δ 10.72 (br s, 1H), 7.96 (d, J = 8.66Hz, 2H), 7.73 (s, 1H), 7.48 (d, J = 8.67Hz, 2H), 7.38 (d, J = 7.16Hz, 1H), 6.34 (d, J = 7.15Hz, 1H), 2.85 (s, 1H), 0.84 (m, 2H), 0.63-0.66 (m, 2H)
M^-(ES): 366.1; M^+(ES): 368.2; HPLC (max plot) 99.4% ; Rt: 3.22 min.

Example 83: [4-(3,4-dichlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile



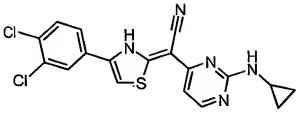
Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)[4-(3,4-dichlorophenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile and 1-(3-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 5 min at 155°C in EtOH as a yellow powder (64%).
^{1}H NMR (DMSO-d_6) δ 10.8 (br s, 1H), 8.18 (s, 1H), 7.97 (d, J = 8.66Hz, 1H), 7.89 (s, 1H), 7.70 (d, J = 8.29Hz, 1H), 7.38 (br s, 1H), 7.37 (d, J = 7.54Hz, 1H), 6.28 (d, J = 7.53Hz, 1H), 3.51 (m, 2H), 3.26-3.36 (m, 4H), 2.22 (t, J = 7.91Hz, 2H), 1.88 (quint, J = 6.79, 2H), 1.82 (quint, J = 6.78 2H)
M^-(ES): 484.8; M^+(ES): 487.1; HPLC (max plot) 97.8% ; Rt: 3.44 min.

Example 84: [4-(3,4-dichlorophenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)[4-(3,4-dichlorophenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine for 5 min at 155°C in EtOH as a yellow powder (30%).
^{1}H NMR (DMSO-d_6) δ 10.82 (br s, 1H), 8.77 (s, 1H), 8.72 (d, J = 5.27Hz, 1H), 8.30 (d, J = 7.91Hz, 1H), 8.18 (d, J= 2.26Hz, 1H), 7.96 (dd, J = 8.29Hz, J = 2.26Hz, 1H), 7.87 (s, 1H), 7.80-7.82 (m, 1H), 7.70 (d, J = 8.29Hz, 1H), 7.58 (br s, 1H), 7.36 (d, J = 7.16Hz, 1H), 6.29 (d, J = 7.15Hz, 1H), 3.89 (m, 2H), 3.13 (t, J = 6.41Hz, 2H)
M^-(ES): 464.3; M^+(ES): 466.8; HPLC (max plot) 96% ; Rt: 2.87 min.

Example 85: [2-(cyclopropylamino)pyrimidin-4-yl][4-(3,4-dichlorophenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile

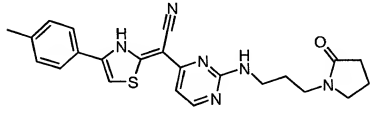


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)[4-(3,4-dichlorophenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile and cyclopropyl amine in the presence of triethylamine for 5 min at 155°C in EtOH as a yellow powder (85%).

^{1}H NMR (DMSO-d_6) δ 10.66 (br s, 1H), 8.16 (s, 1H), 7.94 (d, J = 8.29Hz, 1H), 7.88 (s, 1H), 7.67 (d, J = 8.29Hz, 1H), 7.34 (br t, 1H), 6.33 (d, J = 7.53Hz, 1H), 2.84 (m, 1H), 0.84-0.86 (m, 2H), 0.63 (m, 2H)

M^-(ES): 400.1; M^+(ES): 402.5; HPLC (max plot) 99.9% ; Rt: 3.64 min.

Example 86: [4-(4-methylphenyl)-1,3-thiazol-2(3H)-ylidene](2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

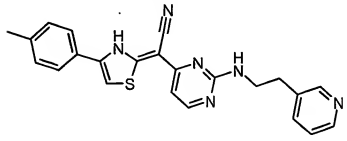


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)[4-(4-methylphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile and 1-(3-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 5 min at 155°C in EtOH as a yellow powder (70%).

^{1}H NMR (DMSO-d_6) δ 10.79 (br s, 1H), 7.82 (d, J = 8.29Hz, 2H), 7.6 (s, 1H), 7.37 (s, 1H), 7.35 (d, J = 7.54Hz, 1H), 7.23 (d, J = 7.91Hz, 2H), 6.27 (d, J = 7.53Hz, 1H), 3.5 (m, 2H), 3.26-3.36 (m, 4H), 2.32 (s, 3H), 2.21 (t, J = 7.53Hz, 2H), 1.92 (quint, J = 7.14, 2H), 1.81 (quint, J = 7.17, 2H)

M^-(ES): 431.1; M^+(ES): 433.2; HPLC (max plot) 97% ; Rt: 2.87 min.

Example 87: [4-(4-methylphenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

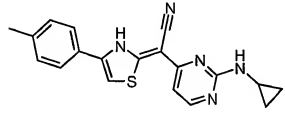


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)[4-(4-methylphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine for 5 min at 155°C in EtOH as a yellow powder (64.8%).

^{1}H NMR (DMSO-d_6) δ 10.75 (br s, 1H), 8.78 (s, 1H), 8.73 (d, J = 5.65Hz, 1H), 8.33 (d, J = 7.91Hz, 1H), 7.87 (s, 1H), 7.84 (d, J = 7.91Hz, 2H), 7.58 (s, 1H), 7.53 (br s, 1H), 7.34 (d, J = 7.16Hz, 1H), 7.23 (d, J = 8.29Hz, 2H), 6.28 (d, J = 7.16Hz, 1H), 3.9 (m, 2H), 3.14 (t, J = 6.32Hz, 2H), 2.33 (s, 3H)

M^-(ES): 413.2; M^+(ES): 413.2; HPLC (max plot) 95% ; Rt: 2.26 min.

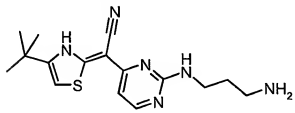
Example 88: [2-(cyclopropylamino)pyrimidin-4-yl][4-(4-methylphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)[4-(4-methylphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile and cyclopropyl amine in the presence of triethylamine for 5 min at 155°C in EtOH as a yellow powder (55%).

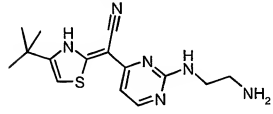
^{1}H NMR (DMSO-d_6) δ 10.71 (br s, 1H), 8.01 (br s, 1H), 7.80 (d, J = 7.91Hz, 2H), 7.6 (s, 1H), 7.39 (br s, 1H), 7.23 (d, J = 7.91Hz, 2H), 6.34 (d, J = 7.15Hz, 1H), 2.86 (br s, 1H), 2.32 (s, 3H), 0.78-0.82 (m, 2H), 0.60-0.63 (m, 2H)
M^-(ES): 346.2; M^+(ES): 348.2; HPLC (max plot) 98.4% ; Rt: 3.08 min.

Example 89 : {2-[(3-aminopropyl)amino]pyrimidin-4-yl}(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-chloropyrimidin-4-yl)acetonitrile and 1,3-diaminopropane in the presence of triethylamine for 4 min at 155°C in EtOH (95.6%).
^{1}H NMR (DMSO-d_6) δ 7.45 (d, J = 6Hz, 1H), 6.39 (s, 1H), 6.11 (d, J = 6Hz, 1H), 3.60-3.24 (m, 2H+2H exchangeable), 2.82-2.77 (m, 2H) , 1.80-1.76 (m, 2H), 1.24 (s, 9H).
HPLC (max plot) 89% ; Rt: 1.78 min.

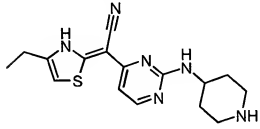
Example 90 : {2-[(2-aminoethyl)amino]pyrimidin-4-yl}(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-chloropyrimidin-4-yl)acetonitrile and 1,2-diaminoethane in the presence of triethylamine for 4 min at 155°C in EtOH (83.7%).

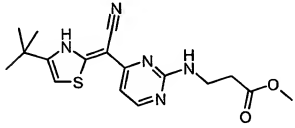
^{1}H NMR (DMSO-d6) δ 7.46 (d, J = 6Hz, 1H), 6.43 (s, 1H), 6.16 (d, J = 6Hz, 1H), 3.60-3.25 (2H+2H exchangeable), 3.00-2.96 (m, 2H), 1.24 (s, 9H).
M^-(ES): 315.2; M^+(ES): 317.2; HPLC (max plot) 89% ; Rt: 1.64 min.

Example 91 : {2-[(piperidin-4-yl)amino]pyrimidin-4-yl}(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1-(tert-butoxycarbonyl)-aminopiperidine in the presence of triethylamine for 6 min at 155°C in EtOH (84.2%).
^{1}H NMR (DMSO-d6) δ 10.26 (br s, 1H, exchangeable), 7.80 (br s, 1H, exchangeable), 7.35-7.25 (m, 1H), 6.85 (s, 1H), 6.21 (d, J = 7.2 Hz, 1H), 4.25-4.0 (br s, 1H), 4.00-3.80 (m, 2H), 3.05-2-80 (m, 2H), 2.70-2.55 (m, 2H), 2.10-1.75 (m, 2H), 1.55-1.25 (m, 11H [9+2]), 1.24-1.10 (m, 3H).
M^+(ES): 429; HPLC (max plot) 79% ; Rt: 3.12 min.
The Boc protected tert-butyl 4-({4-[cyano(4-ethyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)piperidine-1-carbamate was treated with a solution of 20% TFA in DCM overnight at rt, affording the title compound as a diTFA salt after evaporation of the solvent (52.5%).
^{1}H NMR (DMSO-*d6*) δ 11.57 (br s, 1H, exchangeable), 9.00-8.15 (m, 4H, exchangeable), 8.10-7.90 (m, 1H), 7.62-7.55 (m, 1H), 6.93 (s, 1H), 6.39 (d, J = 6.8Hz,1H), 4.30-4.20 (m, 1H), 3.45-2.85 (m, 2+2H), 2.80-2.55 (m, 2H),2.35-1.50 (m, 2+2H), 1.25-1.15 (m, 3H).
M^+(ES): 330.3; HPLC (max plot) 76.8% ; Rt: 1.47 min.

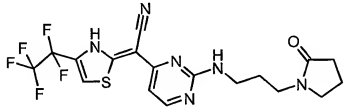
Example 92 : methyl N-{4-[(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(cyano)methyl]pyrimidin-2-yl}-beta-alaninate



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-chloropyrimidin-4-yl)acetonitrile and Beta-alanine methyl ester hydrochloride in the presence of triethylamine for 4 min at 155°C in EtOH (63.6%).

M^-(ES): 358; M^+(ES): 360; HPLC (max plot) 80% ; Rt: 2.68 min.

Example 93 : (2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)[4-(pentafluoroethyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile

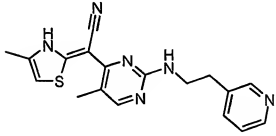


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)[4-(pentafluoroethyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile and 1-(3-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 4 min at 155°C in EtOH (99%).

^{1}H NMR (DMSO-d6) δ 10.94 (s, 1H); 7.97 (s, 1H); 7.52 (s, 1H); 7.42 (d, *J*=7.5Hz, 1H); 6.30 (d, *J*=7.2Hz, 1H); 3.50 (m, 2H); 3.31 (m, 4H); 2.20 (t, *J*=7.5Hz, 2H); 1.89 (quint, *J*=7.5Hz, 2H); 1.81(quint, *J*=7.2Hz, 2H)

M^+(ES): 461; HPLC (max plot) 99.8% ; Rt: 3.70 min.

Example 94 : {5-methyl-2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

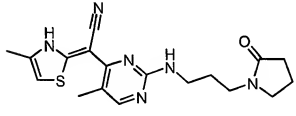


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine for 15 min at 155°C in EtOH (66.6%).

^{1}H NMR (DMSO-d6) δ 8.65 (d, *J*=1.6Hz, 1H); 8.61 (dd, *J*=1.6Hz, *J*= 5.3Hz, 1H); 8.09 (d, *J*=7.5Hz, 1H); 7.67 (dd, *J*=5.6Hz, *J*=7.5Hz, 1H); 7.56 (s, 1H); 7.04 (s, 1H); 3.82 (s, 2H); 3.05 (t, *J*=6.8Hz, 2H); 2.34 (s, 3H); 2.33 (s, 3H)

M^+(ES): 351; HPLC (max plot) 100% ; Rt: 1.52 min.

Example 95 : (5-methyl-2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

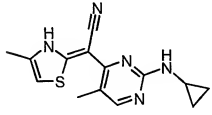


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1-(3-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 16 min at 155°C in EtOH (67.2%).

^{1}H NMR (DMSO-d6) δ 7.78 (br s, 1H); 7.52 (s, 1H); 7.05 (s, 1H); 3.44 (br s, 2H); 3.34 (t, *J*=Hz, 2H); 3.28 (t, 2H); 2.35 (s, 3H); 2.32 (s, 3H); 2.20 (t, *J*= 8Hz, 2H); 1.90 (quint, *J*= 7.5Hz, 2H); 1.80 (quint, J=7.2Hz, 2H).

M^+(ES): 371; HPLC (max plot) 97.3% ; Rt: 2.10 min.

Example 96: [2-(cyclopropylamino)-5-methylpyrimidin-4-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

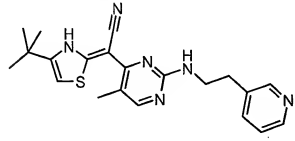


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclopropylamine in the presence of triethylamine for 22 min at 155°C in EtOH (65.7%).

^{1}H NMR (DMSO-d6) δ 13 (br s, 1H); 8.49 (s, 1H); 7.57 (s, 1H); 7.07 (s, 1H); 2.78 (s, 1H); 2.34 (s, 6H); 0.89 (m, 2H); 0.65 (m, 2H)

M^+(ES): 286; HPLC (max plot) 100% ; Rt: 2.15 min.

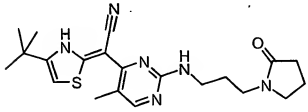
Example 97: (4-tert-butyl-1,3-thiazol-2(3H)-ylidene){5-methyl-2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-chloro-5-methylpyrimidin-4-yl)acetonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine for 28 min at 155°C in EtOH (70.8%).

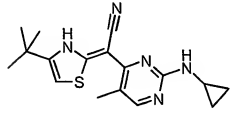
^{1}H NMR (DMSO-d6) δ 8.72 (br d, 1H), 8.69-8.68 (m, 1H), 8.22 (d, J = 7.9Hz, 1H), 7.79 (dd, J = 5.6Hz, J = 7.9Hz, 1H), 7.45 (br s, 1H), 7.25 (s, 1H), 6.84 (s, 1H), 3.86-3.78 (m, 2H), 3.09-3.04 (m, 2H), 2.27 (s, 3H), 1.28 (s, 9H).
M^+(ES): 393.3; HPLC (max plot) 93.9% ; Rt: 2.08 min.

Example 98: (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(5-methyl-2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-chloro-5-methylpyrimidin-4-yl)acetonitrile and 1-(3-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 20 min at 155°C in EtOH (64.9%).
^{1}H NMR (DMSO-*d6*) δ 7.50-7.32 (m, 2H), 6.92 (s, 1H), 3.46-3.44 (m, 2H), 3.38-3.24 (m, 4H), 2.22 (s, 3H), 2.19 (t, J = 7.9Hz, 2H), 1.94-1.72 (m, 4H), 1.30 (s, 9H)
M^+(ES): 413.3; HPLC (max plot) 98.8% ; Rt: 2.78 min.

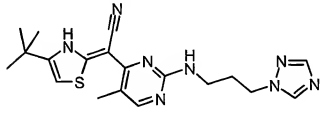
Example 99 : (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)[2-(cyclopropylamino)-5-methylpyrimidin-4-yl]acetonitrile



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-chloro-5-methylpyrimidin-4-yl)acetonitrile and cyclopropylamine in the presence of triethylamine for 20 min at 155°C in EtOH (70.9%).

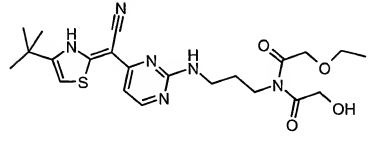
^{1}H NMR (DMSO-*d6*) δ 8.11 (br s, 1H), 7.36 (s, 1H), 6.96 (s, 1H), 2.82-2.72 (m, 1H), 2.31 (s, 3H), 1.31 (s, 9H), 0.88-0.81 (m, 2H), 0.64-0.59 (m, 2H)
M^+(ES):328.2; HPLC (max plot) 99.6% ; Rt: 2.82 min.

Example 100 : (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(5-methyl-2-{[3-(1H-1,2,4-triazol-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-chloro-5-methylpyrimidin-4-yl)acetonitrile and HBr salt of 1-(3'-aminopropyl)-1H-1,2,4-triazole in the presence of triethylamine for 20 min at 155°C in EtOH (23.3%).
^{1}H NMR (DMSO-*d6*) δ 8.53 (s, 1H), 7.98 (s, 1H), 7.54-7.22 (m, 2H,exchangeable), 6.90 (s, 1H), 4.28 (t, J = 6.8Hz, 2H), 3.48-3.46 (m, 2H), 2.28 (s, 3H), 2.16-2.07 (m, 2H), 1.30 (s, 9H)
M^+(ES): 397.3; HPLC (max plot) 99.7% ; Rt: 2.50 min.

Example 101: N-[3-({4-[(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(cyano)methyl]pyrimidin-2-yl}amino)propyl]-2-ethoxy-N-glycoloylacetamide



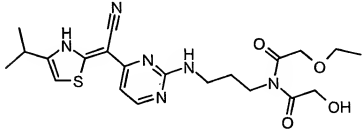
Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-chloropyrimidin-

4-yl)acetonitrile and 4-(3-aminopropyl)morpholine-3,5-dione in the presence of triethylamine for 30 min at 155°C in EtOH (27.6%).

^{1}H NMR (DMSO-*d6*) δ 10.8 (br s, 1H), 7.92 (br t, 1H, exchangeable), 7.58-7.32 (m, 2H, including 1 exchangeable), 6.87 (s, 1H), 6.31 (br d, 1H), 4.17 (s, 2H), 4.11 (q, J = 7.2Hz, 2H), 3.95 (s, 2H), 3.55-3.45 (m, 2H), 3.24-3.20 (m, 2H), 1.78-1.74 (m, 2H), 1.28 (s, 9H), 1.18 (t, J = 7.2Hz, 3H)

M^+(ES): 475.2; HPLC (max plot) 95.7% ; Rt: 2.72 min.

Example 102 : N-[3-({4-[cyano(4-isopropyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)propyl]-2-ethoxy-N-glycoloylacetamide

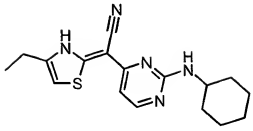


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-isopropyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 4-(3-aminopropyl)morpholine-3,5-dione in the presence of triethylamine for 5 min at 155°C in EtOH (40%).

^{1}H NMR (DMSO-*d6*) δ 11.30 (br s, 1H), 7.81-7.61 (m, 2H, exchangeable), 7.46 (br d, 1H), 6.83 (s, 1H), 6.26 (br d, 1H), 4.02 (s, 2H), 3.96 (q, J = 7.2Hz, 2H), 3.80 (s, 2H), 3.42-3.28 (m, 2H), 3.10-3.03 (m, 2H), 2.92-2.88 (m, 1H), 1.64-1.60 (m, 2H), 1.08 (d, J = 6.7Hz, 6H), 1.03 (t, J = 7.2Hz, 3H).

M^+(ES): 461.2; HPLC (max plot) 97.5% ; Rt: 2.57 min.

Example 103 : [2-(cyclohexylamino)pyrimidin-4-yl](4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

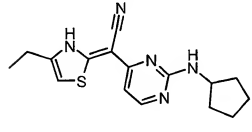


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclohexylamine in the presence of triethylamine for 4 min at 155°C in EtOH (75.7%).

^{1}H NMR (DMSO-*d6*) δ 11.40 (br s, 1H), 7.99 (br s, 1H, exchangeable), 7.65 (br d, 1H), 7.11 (s, 1H), 6.43 (d, *J* = 7.2Hz, 1H), 4.08-3.95 (m, 1H), 2.72-2.65 (m, 2H), 2.00-1.97 (m, 2H), 1.76-1.71 (m, 2H), 1.63-1.59 (m, 1H), 1.39-1.28 (m, 5H), 1.23-1.18 (m, 3H)

M^+(ES): 328.2; HPLC (max plot) 96.4% ; Rt: 3.04 min.

Example 104 : [2-(cyclopentylamino)pyrimidin-4-yl](4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

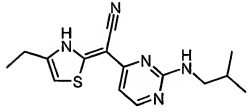


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclopentylamine in the presence of triethylamine for 4 min at 155°C in EtOH (78.2%).

^{1}H NMR (DMSO-*d6*) δ 8.28 (br s, 1H exchangeable), 7.95 (br s, 1H exchangeable), 7.70 (d, *J* = 7.1Hz, 1H), 7.07 (s, 1H), 6.46 (d, *J* = 7.1Hz, 1H), 4.53-3.98 (m, 1H), 2.73-2.66 (m, 2H), 2.06-2.02 (m, 2H), 1.70-1.55 (m, 6H), 1.22-1.18 (m, 3H)

M^+(ES): 314.2; HPLC (max plot) 97.2% ; Rt: 2.82 min.

Example 105: (4-ethyl-1,3-thiazol-2(3H)-ylidene)[2-(isobutylamino)pyrimidin-4-yl]acetonitrile

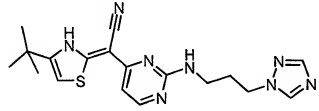


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and isobutylamine in the presence of triethylamine for 4 min at 155°C in EtOH (91.2%).

^{1}H NMR (DMSO-*d6*) δ 7.97 (br s, 1H exchangeable), 7.51 (d, *J* = 7.2 Hz, 1H), 6.91 (s, 1H), 6.26 (d, *J* = 7.2Hz, 1H), 3.19-3.08 (m, 2H), 2.51-2.43 (m, 2H),1.76-1.67 (m, 1H), 0.97 (t, *J* = 7.6 Hz, 3H), 0.72 (d, *J* = 6.7Hz, 6H)

M^+(ES): 302.3; HPLC (max plot) 100% ; Rt: 2.75 min.

Example 106 : (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-{[3-(1H-1,2,4-triazol-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

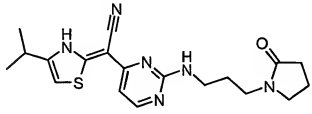


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-chloropyrimidin-4-yl)acetonitrile and the HCl salt of 3-(1H-1,2,4-triazol-1-yl)propan-1-amine in the presence of triethylamine for 8 min at 155°C in EtOH (88.6%).

^{1}H NMR (DMSO-*d6*) δ 8.55 (s, 1H), 8.00 (s, 1H), 7.53 (br d, 1H), 6.92 (s, 1H), 6.38 (d, *J*=7.1Hz, 1H), 4.30 (t, *J*=6.8Hz, 2H), 3.51-3.49 (m, 2H), 2.18-2.09 (m, 2H), 1.31 (s, 9H).

M^+(ES): 383.3; HPLC (max plot) 99.4% ; Rt: 2.34 min.

Example 107: (4-isopropyl-1,3-thiazol-2(3H)-ylidene)(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

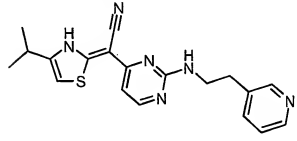


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-isopropyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1-(3-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 4 min at 155°C in EtOH (57%).

^{1}H NMR (DMSO-*d6*) δ 8.00-7.45 (m, 2H, 1 exchangeable), 6.94 (s, 1H), 6.38 (d, J = 7.1 Hz, 1H), 3.65-3.15 (m, 6H, [2+2+2]), 3.10-2.95 (m, 1H), 2.25-2.10 (m, 2H), 2.00-1.65 (m, 4H, [2+2]), 1.23 (d, J = 7.1 Hz, 6H).

M^+(ES): 385; HPLC (max plot) 99.7% ; Rt: 2.43 min.

Example 108: (4-isopropyl-1,3-thiazol-2(3H)-ylidene){2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

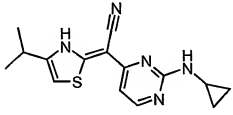


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-isopropyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 3-(2-aminoethyl)pyridine in the presence of Triethylamine for 4 min at 155°C in EtOH (88.6%).

^{1}H NMR (DMSO-*d6*) δ 8.67 (s, 1H), 8.62 (d, J = 5.3Hz, 1H), 8.09 (d, J = 7.9Hz, 1H), 7.93 (br s, 1H, exchangeable), 7.70-7.50 (m, 2H), 6.95 (s, 1H), 6.40 (d, J = 7.1 Hz, 1H), 3.95-3.75 (m, 2H), 3.20-2.95 (m, 3H [2+1]), 1.23 (d, J = 6.8 Hz, 6H).

M^+(ES): 365; HPLC (max plot) 97% ; Rt: 1.74 min.

Example 109: [2-(cyclopropylamino)pyrimidin-4-yl](4-isopropyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

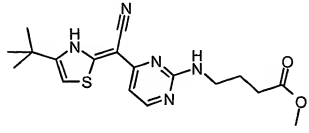


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-isopropyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclopropylamine in the presence of triethylamine for 4 min at 155°C in EtOH (87.8%).

^{1}H NMR (DMSO-*d6*) δ 11.90 (br s, 1H, exchangeable), 8.60-8.40 (br s, 1H, exchangeable), 7.67 (d, J = 6Hz, 1H), 7.02 (s, 1H), 6.47 (d, J = 6.8 Hz, 1H), 3.15-2.95 (m, 1H), 1.23 (d, J = 6.8 Hz, 6H), 0.95-0.85 (m, 2H), 0.68-0.63 (m, 2H).

M^+(ES): 300; HPLC (max plot) 99.8% ; Rt: 2.49min.

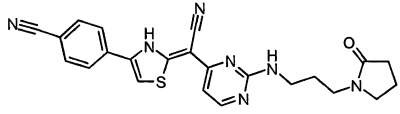
Example 110 : methyl 4-({4-[(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(cyano)methyl]pyrimidin-2-yl}amino)butanoate



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-chloropyrimidin-4-yl)acetonitrile and the HCl salt of methyl 4-aminobutyrate in the presence of triethylamine for 4 min at 155°C in EtOH (56.8%).

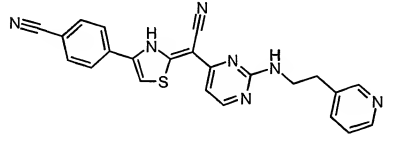
^{1}H NMR (DMSO-*d6*) δ 10.9 (br s, 1H, exchangeable), 7.90-7.35 (m, 2H, including 1 exchangeable), 6.92 (s, 1H), 6.34 (d, *J* = 6.8Hz, 1H), 3.65-3.4 (m, 4H [3+1]), 2.41 (t, *J* = 7.2 Hz), 1.87 (quint, *J* = 7.2 Hz, 2H), 1.29 (s, 9H).
M^+(ES): 374; HPLC (max plot) 96.5% ; Rt: 2.78 min.

Example 111 : 4-{2-[cyano(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)methylene]-2,3-dihydro-1,3-thiazol-4-yl}benzonitrile



Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from 4-{2-[(2-chloropyrimidin-4-yl)(cyano)methylene]-2,3-dihydro-1,3-thiazol-4-yl}benzonitrile and 1-(3-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 5 min at 155°C in EtOH (50%).
^{1}H NMR (DMSO-*d6*) δ 10.8 (s, 1H) ; 8.14 (d, *J* = 8.29Hz, 2H), 7.97 s, 1H), 7.87 (d, *J* = 8.29Hz, 2H), 7.37 (s, 1H), 7.35 (d, *J* = 7.16Hz, 1H), 6.28 (d, *J* = 7.53Hz, 1H), 3.5 (m, 2H), 3.34 (m, 4H), 2.21 (t, *J* = 7.9Hz, 2H), 1.9 (t, *J* = 7.92Hz, 2H), 1.81 (t, *J* = 6.7Hz, 2H).
M^-(ES): 442.3; M^+(ES): 444.3; HPLC (max plot) 97% ; Rt: 2.79 min.

Example 112 : 4-[2-(cyano{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}methylene)-2,3-dihydro-1,3-thiazol-4-yl]benzonitrile



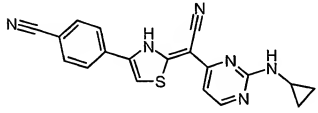
Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from 4-{2-[(2-chloropyrimidin-4-yl)(cyano)methylene]-2,3-

dihydro-1,3-thiazol-4-yl}benzonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine for 5 min at 155°C in EtOH (65%).

^{1}H NMR (DMSO-*d6*) δ 10.8 (s, 1H), 8.76 (s, 1H), 8.71 (d, *J* = 4.14, 1H), 8.3 (d, *J* = 8.29Hz, 1H), 8.16 (d, *J* = 8.29Hz, 2H), 7.95 (s, 1H), 7.9 (d, *J* = 8.67Hz, 2H), 7.86 (d, 1H), 7.56 (s, 1H), 7.37 (d, *J* = 7.15Hz, 1H), 6.3 (d, *J* = 7.16Hz, 1H), 3.89 (m, 2H), 3.13 (t, *J* = 6.78Hz, 2H).

M^-(ES): 422.2; M^+(ES): 424.1; HPLC (max plot) 92.6% ; Rt: 2.25 min.

Example 113: 4-(2-{cyano[2-(cyclopropylamino)pyrimidin-4-yl]methylene}-2,3-dihydro-1,3-thiazol-4-yl)benzonitrile

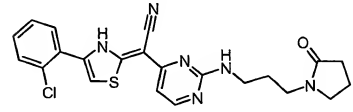


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from 4-{2-[(2-chloropyrimidin-4-yl)(cyano)methylene]-2,3-dihydro-1,3-thiazol-4-yl}benzonitrile and cyclopropylamine in the presence of triethylamine for 5 min at 155°C in EtOH (63.6%).

^{1}H NMR (DMSO-*d6*) δ 10.68 (s, 1H), 8.14 (d, *J* = 8.28Hz, 2H), 7.96 (s, 1H), 7.89 (d, *J* = 8.29Hz, 2H), 7.34 (d, 1H), 6.34 (d, *J* = 7.15Hz, 1H), 2.85 (m, 1H), 0.84 (m, 2H), 0.62 (m, 2H).

M^-(ES): 357.2; M^+(ES): 359.2; HPLC (max plot) 98.3% ; Rt: 2.92 min.

Example 114 : [4-(2-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

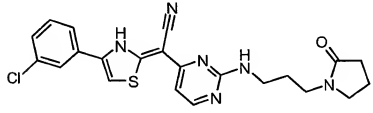


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from [4-(2-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-chloropyrimidin-4-yl)acetonitrile and 1-(3-aminopropyl)-2-pyrrolidinone in the presence of triehtylamine for 5 min at 155°C in EtOH (63.4%).

^{1}H NMR (DMSO-*d6*) δ 10.98 (s, 1H), 7.92 (d, J = 7.54Hz, 1H), 7.68 (s, 1H), 7.56 (d, 3H), 7.38 (m, 3H), 6.3 (d, J = 7.16Hz, 1H), 3.51 (m, 2H), 3.31 (m, 4H), 2.2 (t, J = 7.9Hz, 2H), 1.94-1.79(m, 4H).

M^-(ES): 450.8; M^+(ES): 453.2; HPLC (max plot) 97.1% ; Rt: 2.83 min.

Example115 : [4-(3-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

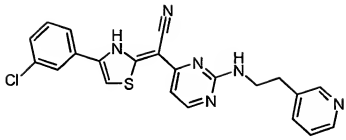


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from [4-(3-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-chloropyrimidin-4-yl)acetonitrile and 1-(3-aminopropyl)-2-pyrrolidinone in the presence of triethylamine for 5 min at 155°C in EtOH (66.3%).

^{1}H NMR (DMSO-*d6*) δ 10.8 (s, 1H), 8.00 (s, 1H), 7.92 (d, J = 7.53Hz, 1H), 7.82 (s, 1H), 7.47 (m, 2H), 7.36 (br d, 2H), 6.29 (d, J = 7.53Hz, 1H), 3.52 (m, 2H), 3.35-3.26 (m, 4H), 2.21 (t, J = 7.54Hz, 2H), 1.92 (quint, J = 7.53Hz, 2H), 1.84 (quint, J = 6.78Hz, 2H).

M^-(ES): 451.1; M^+(ES): 453.1; HPLC (max plot) 97.8% ; Rt: 3.06 min.

Example 116 : [4-(3-chlorophenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

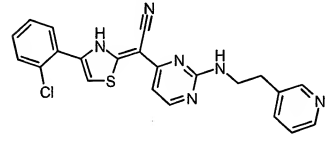


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from [4-(3-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-chloropyrimidin-4-yl)acetonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine for 5 min at 155°C in EtOH (57.4%).

^{1}H NMR (DMSO-*d6*) δ 10.9 (s, 1H), 8.82 (s, 1H), 8.78 (d, *J* = 5.08Hz, 1H), 8.41(d, *J* = 8.1Hz, 1H), 8.00 (s, 1H), 7.95 (d, *J* = 7.72Hz, 2H), 7.8 (s, 1H), 7.63 (s, 1H), 7.46 (t, J = 7.7Hz, 1H), 7.37 (d, *J* = 7.17Hz, 2H), 6.31 (d, *J* = 7.34Hz, 1H), 3.91 (m, 2H), 3.16 (br t, 2H).

M^-(ES): 431.1; M^+(ES): 432.9; HPLC (max plot) 95.5% ; Rt: 2.45 min.

Example 117: [4-(2-chlorophenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}acetonitrile

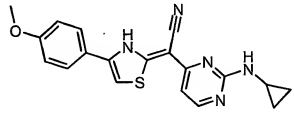


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from [4-(2-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-chloropyrimidin-4-yl)acetonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine for 5 min at 155°C in EtOH (34.1%).

^{1}H NMR (DMSO-*d6*) δ 10.74 (s, 1H), 8.71 (s, 1H), 8.66 (d, *J* = 4.52Hz, 1H), 8.26 (d, *J* = 8.67Hz, 1H), 7.89 (d, *J* = 7.53Hz, 1H), 7.79 (m, 1H), 7.61 (s, 1H), 7.49 (d, *J* = 7.53Hz, 1H), 7.45-7.40 (m, 1H), 7.33 (m, 2H), 6.25 (d, *J* = 7.54Hz, 1H), 3.84 (m, 2H), 3.08 (br t, 2H).

M^-(ES): 431.1; M^+(ES): 433.1; HPLC (max plot) 91.6% ; Rt: 2.16 min.

Example 118 : [2-(cyclopropylamino)pyrimidin-4-yl][4-(4-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile

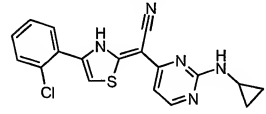


Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from (2-chloropyrimidin-4-yl)[4-(4-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile and cyclopropylamine in the presence of triethylamine for 5 min at 155°C in EtOH (37.9%).

^{1}H NMR (DMSO-*d6*) δ 8.2 (br s, 1H), 7.83 (d, *J* = 8.66Hz, 2H), 7.52 (s, 1H), 7.45 (d, *J* = 7.54Hz, 1H), 6.99 (d, *J* = 9.04Hz, 2H), 6.36 (d, *J* = 9.04Hz, 1H), 3.79 (s, 3H), 2.87 (br s, 1H), 0.87-0.75 (m, 2H), 0.65-0.56 (m, 2H).

M^-(ES): 362.2; M^+(ES): 634.1; HPLC (max plot) 100% ; Rt: 3.00 min.

Example 119: [4-(2-chlorophenyl)-1,3-thiazol-2(3H)-ylidene][2-(cyclopropylamino)pyrimidin-4-yl]acetonitrile



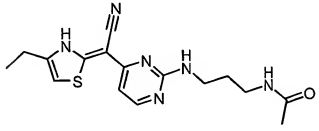
Following the general strategies and protocols outlined in the procedure E, the title compound was obtained from [4-(2-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-chloropyrimidin-4-yl)acetonitrile and cyclopropylamine in the presence of triethylamine for 5 min at 155°C in EtOH (58.5%).

^{1}H NMR (DMSO-*d6*) δ 7.89 (br d, 1H), 7.67 (s, 1H), 7.56 (dd, *J*= 7.16Hz, *J*= 1.89Hz, 1H), 7.37-7.46 (m, 3H), 6.37 (d, *J*= 6.78Hz, 1H), 2.85 (br s, 1H), 2.91-2.75 (m, 2H), 0.70-0.50 (m, 2H).

M^-(ES): 366.1; M^+(ES): 368.1; HPLC (max plot) 100% ; Rt: 3.06 min.

Procedure F

Example 120: N-[3-({4-[cyano(4-ethyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)propyl]acetamide



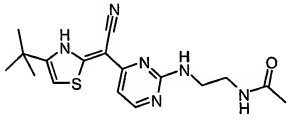
To a solution of {2-[(3-aminopropyl)amino]pyrimidin-4-yl}(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile (165mg, 0.37mmol) in DMA (3mL) were added and Et_3N (0.048mL, 0.37mmol) and acetyl chloride (0.04mL, 0.46mmol) at 0°C. The resulting solution was stirred at 0°C for 3h. The solvent was evaporated under reduced pressure (Genevac) affording the title compound as a crude yellow solid. HPLC (max plot) 92%.

The solid was taken up in DCM and an excess TFA was added. The yellow precipitate formed after addition of ether was filtered off and washed with ether (X3) then dried under vacuum at 40°C. After purification by preparative HPLC then lyophilization, 148 mg of the title compound was obtained as a TFA salt (yellow powder, Y = 87.3%)

^{1}H NMR (DMSO-d_6) δ 7.93-7.90 (m, 2H), 7.65 (br d, 1H), 7.01 (s, 1H), 6.43 (d, *J*= 7.1Hz, 1H), 3.56-3.44 (m, 2H), 3.16-3.10 (m, 2H), 2.69 (q, *J*= 7.5Hz, 2H), 1.78 (s, 3H), 1.75-1.71 (m, 2H), 1.20 (t, *J*= 7.5Hz, 3H).

M^+(ES): 345.2; HPLC (max plot) 99% ; Rt: 1.97 min.

Example 121 : N-[2-({4-[(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(cyano)methyl]pyrimidin-2-yl}amino)ethyl]acetamide

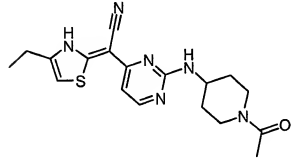


Following the general strategies and protocols outlined in the procedure F, the title compound was obtained from {2-[(2-aminoethyl)amino]pyrimidin-4-yl}(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and acetyl chloride in the presence of triethylamine for 1h30 at 0°C in DMA (58.9%).

^{1}H NMR (DMSO-*d6*) δ 8.01-7.98 (m, 1H, exchangeable), 7.69 (br s, 1H, exchangeable), 7.49 (br d, 1H), 6.88 (s, 1H), 6.36 (d, *J* = 7.1Hz, 1H), 3.67-3.38 (m, 2H), 3.34-3.30 (m, 2H), 1.81 (s, 3H), 1.30 (s, 9H).

M^+(ES): 359.2; HPLC (max plot) 100% ; Rt: 2.24 min.

Example 122: {2-[(1-acetylpiperidin-4-yl)amino]pyrimidin-4-yl}(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

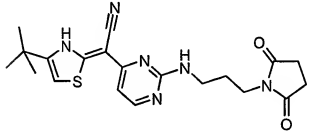


Following the general strategies and protocols outlined in the procedure F, the title compound was obtained from the TFA salt of {2-[(piperidin-4-yl)amino]pyrimidin-4-yl}(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and acetyl chloride in the presence of triethylamine for 1h30 at 0°C to r.t. in DCM (3.8%).

^{1}H NMR (DMSO-*d6*) δ 8.00-7.40 (2 br s, 2H including 1 exchangeable), 7.01 (s, 1H), 6.40 (d, *J* = 6.1H, 1H), 4.40-4.25 (m, 1H), 4.00-3.75 (m, 2H), 3.00-2.60 (m, 7H [2+2+3]), 2.10-1.90 (m, 5H, [2+3]), 1.55-1.10 (m, 5H, [3+2]).
M^+(ES): 371; HPLC (max plot) 99% ; Rt: 2.19 min.

Procedure G

Example 123: (4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(2-{[3-(2,5-dioxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile

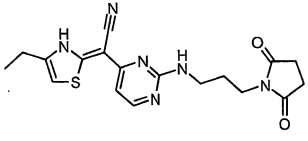


To a suspension of {2-[(3-aminopropyl)amino]pyrimidin-4-yl}(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)acetonitrile (200 mg, 0.61 mmol) in DMA in a microwave tube (X2) were added succinic anhydride (122mg, 1.21 mmol) and NMM (0.133 mL, 1.21 mmol) and after sonication the solution was heated up to 250°C on normal absorption for 15 min. Both tubes were gathered and 10mL of water were added then the suspension was left at 4°C for ON. The solid obtained was filtered off through paper and washed with water (3X) then dried under vacuum at 40C for 5 days, affording the crude title compound as a brown powder. The solid was taken up in DCM then an excess TFA was added. To the black solution was added ether and the suspension was left at 4°C for 2h. The precipitate formed was filtered off then washed with ether (3X), affording 353.9 mg of the title compound as a TFA salt (HPLC (max plot) 92%).
After purification by preparative HPLC then lyophilization, 210 mg of the title compound were obtained as a TFA salt (yellow powder, Y = 33%).

^{1}H NMR (DMSO-d_6) δ 11.0-10.7 (br s, 1H, exchangeable), 7.55-7.35 (m, 2H, including one H exchangeable), 6.87 (s, 1H), 6.32 (d, J= 6.0Hz, 1H), 3.70-3.30 (m, 4H), 2.58 (s, 4H), 1.95-1.70 (m, 2H), 1.29 (s, 9H).

M^-(ES): 411; M^+(ES): 413; HPLC (max plot) 95% ; Rt: 2.50 min.

Example 124: (2-{[3-(2,5-dioxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

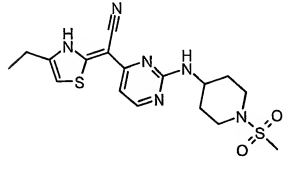


Following the general strategies and protocols outlined in the procedure G, the title compound was obtained from {2-[(3-aminopropyl)amino]pyrimidin-4-yl}(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and succinic anhydride in the presence of NMM for 15 min at 250°C in DMA as a yellow powder (23.6%).

^{1}H NMR (DMSO-d_6) δ 7.88 (s, 1H), 7.64 (br d, 1H), 7.00 (s, 1H), 6.42 (d, J = 7.2Hz, 1H), 3.48-3.43 (m, 4H), 2.69 (q, J = 7.5Hz, 2H), 2.59 (s, 4H), 1.85-1.81 (m, 2H), 1.20 (t, J = 7.5Hz, 3H).

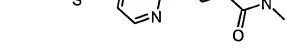
M^+(ES): 385.2; HPLC (max plot) 97.3% ; Rt: 2.11 min.

Example 125 : (4-ethyl-1,3-thiazol-2(3H)-ylidene)(2-{[1-(methylsulfonyl)piperidin-4-yl]amino}pyrimidin-4-yl)acetonitrile trifluoroacetate



To a supension of {2-[(piperidin-4-yl)amino]pyrimidin-4-yl}(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile (102mg, 0.18mmol) in DCM (3mL) were added at 0°C trietylamine (0.09mL, 0.64 mmol) and a solution of methylsulphonyl chloride (0.017mL, 0.22 mmol) in DCM (1 mL). The bright yellow solution was stirred at r.t for 2h. Water was added and the product was extracted with DCM (3X). The organic phase was washed with water (2X) then brine (1X) and dried over $MgSO_4$. After removal of the solvent, the residue was taken up in DCM (1mL) and 20µL of TFA were added. A fluffy precipitate formed upon addition of ether. It was filtered off and washed with ether (3X) then dried under vacuum at 40°C, affording 42.9 mg of the title compound as a TFA salt (yellow fluffy solid, 41%).
^{1}H NMR (DMSO-*d6*) δ 11.3-11.0 (br s, 1H exchangeable), 8.1-7.9 (br s, 1H, exchangeable), 7.70-7.60 (m, 1H), 7.06 (s, 1H), 6.43 (d, J = 7.2 Hz, 1H), 4.17-3.90 (m, 1H), 3.7-3.5 (m, 2H), 3.05-2.85 (m, 5H [2+3]), 2.70 (q, J = 7.9, 7.5 Hz, 2H), 2.15-2.07 (m, 2H), 1.70-1.50 (m, 2H), 1.21 (t, J = 7.5 Hz, 3H).
M^+(ES): 407; HPLC (max plot) 92% ; Rt: 2.29 min.

Example126 : N~3~-{4-[(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(cyano)methyl]pyrimidin-2-yl}-N~1~,N~1~-dimethyl-beta-alaninamide



To a solution of dimethylamine (0.051 mL, 1 mmol) in DCE was added a solution of TMA 2M in hexane (499 mL, 1 mmol) and the mixture was stirred 30 min at r.t. To this solution was added a solution of methyl N-{4-[(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(cyano)methyl]pyrimidin-2-yl}-beta-alaninate (72 mg, 0.2 mmol) in DCE and the mixture was refluxed under inert atmosphere overnight then stirred for a week at r.t. The mixture was diluted with DCM then water was added. The suspension was filtered through celite. The filtrate was washed with aqueous NaHCO3 5% (X2) then brine and it was dried

over MgSO4. The solvent was removed under reduced pressure affording the title compound as yellow solid (HPLC max plot 86%).

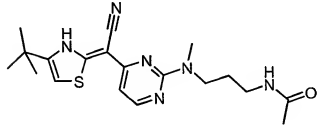
The solid was taken up in DCM and 10µL of TFA were added then ether in large excess. As no precipitation occurred, the solvents were evaporated under reduced pressure. The solid residue obtained was taken up in ether, sonicated then filtered off and washed with ether (2X). It was then dried under vacuum at 40°C ON, affording 38 mg of the title compound as a TFA salt (pale yellow powder Y = 39%).

^{1}H NMR (DMSO-*d6*) δ 7.65-7.45 (m, 2H, including 1 exchangeable), 6.88 (s, 1H), 6.34 (d, *J* = 7.2 Hz, 1H), 3.80-3.70 (m, 1H), 2.91 (s, 3H), 2.84 (s, 3H), 2.67 (t, *J* = 6.0 Hz, 2H), 1.29 (s, 9H).

M^+(ES): 373; HPLC (max plot) 96% ; Rt: 2.50 min.

Procedure H

Example 127 : N-{3-[{4-[(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(cyano)methyl]pyrimidin-2-yl}(methyl)amino]propyl}acetamide



To suspension of N-[3-({4-[(4-tert-butyl-1,3-thiazol-2(3H)-ylidene)(cyano)methyl]pyrimidin-2-yl}amino)propyl]acetamide (290mg, 0.68mmol) in THF (7ml) were added potassium tert-butoxide (91mg, 0.81 mmol) and methyl iodide (0.085mL, 1.35mmol). The resulting mixture was stirred 2h at rt. LC/MS analysis showed the presence two peaks with the same mass in a proportion of 7:3. The THF was evaporated and the residue was taken up in water and extracted with EtOAc (3x). The combined organic layer was washed with brine, dried with $MgSO_4$ and the solvent was evaporated under reduced pressure to give a gummy residue which was the mixture of to compounds of

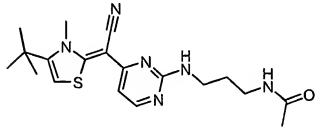
the same mass. It was taken up in DCM and an excess TFA then ether were added to the solution. As no precipitation occurred, the solution was concentrated under reduced pressure and the residue was purified by preparative HPLC to give 93 mg of the title compound as a TFA salt pyrimidine (yellow solid, Y = 27.3%).

^{1}H NMR (DMSO-*d6*) δ 7.94-7.85 (m, 1H, exchangeable), 7.75-7.46 (m, 2H, 1 exchangeable), 6.89 (s, 1H), 6.40 (br d, 1H), 3.61-3.59 (m, 2H), 3.45 (s, 3H), 3.16-3.12 (m, 2H), 1.78 (s, 3H), 1.78-1.70 (m, 2H), 1.30 (s, 9H)

M^+(ES): 387.3; HPLC (max plot) 100% ; Rt: 2.35 min.

HPLC (max plot) 99.3%, rt = 3.24min., LCMS(ES+): 387.27, H-NMR (DMSO) 8.34 (br d, 1H), 7.84-7.75 (m, 1H, exchangeable), 7.52 (br s, 1H, exchangeable), 7.35 (s, 1H), 6.66 (br d, 1H), 3.32-3.21 (m, 2H), 3.08-3.01 (m, 2H), 2.12 (s, 3H), 1.77 (s, 3H), 1.66-1.59 (m, 2H), 1.27 (s, 9H).

Example 128 : N-[3-({4-[(4-tert-butyl-3-methyl-1,3-thiazol-2(3H)-ylidene)(cyano)methyl]pyrimidin-2-yl}amino)propyl]acetamide



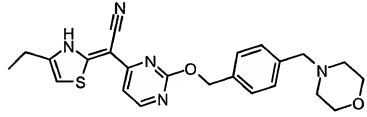
Following the general strategies and protocols outlined in the procedure H, 70 mg the title compound were obtained after purification of the second product obtained during the synthesis of Example 115 (orange oil, 20.6%).

^{1}H NMR (DMSO-*d6*) δ 8.34 (br d, 1H), 7.84-7.75 (m, 1H, exchangeable), 7.52 (br s, 1H, exchangeable), 7.35 (s, 1H), 6.66 (br d, 1H), 3.32-3.21 (m, 2H), 3.08-3.01 (m, 2H), 2.12 (s, 3H), 1.77 (s, 3H), 1.66-1.59 (m, 2H), 1.27 (s, 9H).

M^+(ES): 387.3; HPLC (max plot) 99.3% ; Rt: 3.24 min.

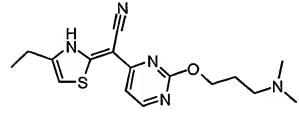
Procedure I

Example 129: (4-ethyl-1,3-thiazol-2(3H)-ylidene)(2-{[4-(morpholin-4-ylmethyl)benzyl]oxy}pyrimidin-4-yl)acetonitrile



To a suspension of NaH (99 mg, 2.27 mmol) in ACN (4 mL) was added a solution of N-(4-hydroxymethylbenzyl)morpholine (313 mg, 1.51 nmol) in ACN (4 mL). The mixture was stirred 1h at rt. Then (2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile (200mg, 0.76 mmol) was added portionwise. The resulting mixture was heated up at 80°C for 5h. After cooling down to rt the ACN was evaporated. EtOAc (5mL) was added to the residue. After one night at 4°C, the yellow solid was filtered off affording the title compound as a free base (HPLC (max plot) 73.9%). The solid was taken up in DCM and excess TFA then ether were added. The precipitate formed was fitered off, washed with ether (3X) then dried under reduced pressure at 40°C overnight, affording 409 mg of the title compound as a diTFA salt (Yellow powder, Y = 81.1%)
^{1}H NMR (DMSO-d_6) δ 10.26 (br s, 1H),7.76 (br d, 1H), 7.61 (d, J = 7.9Hz, 2H), 7.53 (d, J = 7.9Hz, 2H), 6.90 (s, 1H), 6.61 (br d, 1H), 5.64 (s, 2H), 4.36 (s, 2H), 4.03-3.85 (m, 2H), 3.74-3.53 (m, 2H), 3.32-3.04 (m, 4H), 2.66 (q, J = 7.5Hz, 2H), 1.19 (br t, 3H).
M^+(ES): 436.0; HPLC (max plot) 98.2% ; Rt: 1.82 min.

Example 130: {2-[3-(dimethylamino)propoxy]pyrimidin-4-yl}(4-ethyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



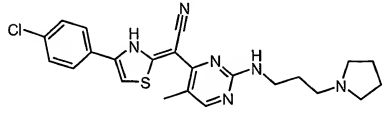
Following the general strategies and protocols outlined in the procedure I, the title compound was obtained from 2-chloropyrimidin-4-yl)(4-ethyl-1,3-thiazol-2(3H)-

ylidene)acetonitrile and 3-dimethylamino-1-propanol in the presence of sodium hydride for 4 h at rt then 80°C in ACN as a yellow powder (61%).
^{1}H NMR (DMSO-d_6) δ 9.51 (br s, 1H), 7.75 (br d, 1H), 6.91 (s, 1H), 6.59 (br d, 1H), 4.60-4.56 (m, 2H), 3.25-3.20 (m, 2H), 2.81 (s, 6H), 2.67 (q, J = 7.5 Hz, 2H), 2.19-2.15 (m, 2H), 1.20 (t, J = 7.5 Hz, 3H).
M(ES): 330.3; HPLC (max plot) 99.9% ; Rt: 1.29 min.

General Procedure J

10 mg of Building Blocks were dissolved in 0.3 mL of DMA. Et_3N (4eq.) and the amines (4 eq.) dissolved in DMA (0.3mL) were then added to the reaction mixtures and the plate was sealed and heated in a microwave (Mars 5) as follows: 2 plates at a time were heated 4 min at 300 Watts and then left to cool down for 10 min. This was repeated 4 times. The reaction mixtures were then transferred into a 2 mL plate and the solvent was removed in the Genevac. Work up: 1 mL of water/CH_3COOH (2%) was then added and the plate was shaken for 3h00. The aqueous layer was removed using the Zymark, leaving the solid behind. This solid was further washed with water (2X). 1 mL of MeOH/TFA (20%) was added to the plates, which were shaken at rt for 48h and the supernatant was collected using the Lissy. Analytical plates were made and the solvents were removed in the Genevac.

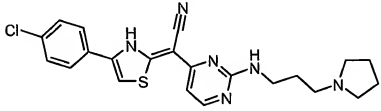
Example 131: [4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene]{5-methyl-2-[(3-pyrrolidin-1-ylpropyl)amino]pyrimidin-4-yl}acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)[4-(4-chlorophenyl)-1,3-

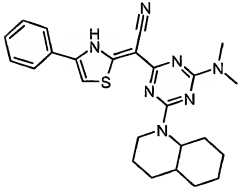
thiazol-2(3H)-ylidene]acetonitrile and 1-(3-aminopropyl)pyrrolidine in the presence of triethylamine in DMA.
M^+(ES): 453.2; LC (215nm): 91%

Example 132: [4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(3-pyrrolidin-1-ylpropyl)amino]pyrimidin-4-yl}acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from [4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-chloropyrimidin-4-yl)acetonitrile and 1-(3-aminopropyl)pyrrolidine in the presence of triethylamine in DMA.
M^+(ES): 439.2; LC (215nm): 86.8%

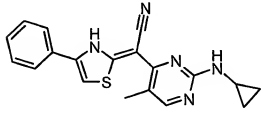
Example 133: [4-(dimethylamino)-6-(octahydroquinolin-1(2H)-yl)-1,3,5-triazin-2-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from [4-chloro-6-(dimethylamino)-1,3,5-triazin-2-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and decahydroquinoline in the presence of triethylamine in DMA.

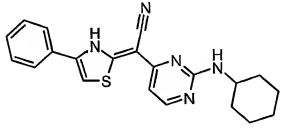
M^+(ES): 460.2; LC (215nm): 91.4%

Example 134: [2-(cyclohexylamino)-5-methylpyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



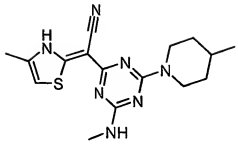
Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclohexamine in the presence of triethylamine in DMA.
M^+(ES): 390.2; LC (215nm): 67.7%

Example 135: [2-(cyclohexylamino)pyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclohexamine in the presence of triethylamine in DMA.
M^+(ES): 376.11; LC (215nm): 92%

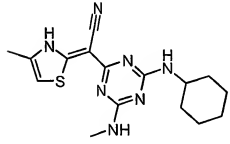
Example 136: [4-(methylamino)-6-(4-methylpiperidin-1-yl)-1,3,5-triazin-2-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from [4-chloro-6-(methylamino)-1,3,5-triazin-2-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 4-methylpiperidine in the presence of triethylamine in DMA.

M^+(ES): 344.1; LC (215nm): 90.7%

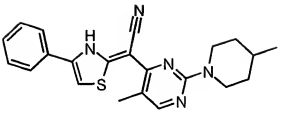
Example 137: [4-(cyclohexylamino)-6-(methylamino)-1,3,5-triazin-2-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from from [4-chloro-6-(methylamino)-1,3,5-triazin-2-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclohexamine in the presence of triethylamine in DMA.

M^+(ES): 344.1; LC (215nm): 97.9%

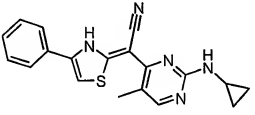
Example 138: [5-methyl-2-(4-methylpiperidin-1-yl)pyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 4-methylpiperidine in the presence of triethylamine in DMA.

M^+(ES): 390.1; LC (215nm): 86.2%

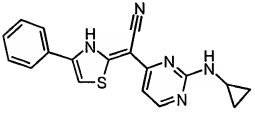
Example 139: [2-(cyclopropylamino)-5-methylpyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclopropylamine in the presence of triethylamine in DMA.

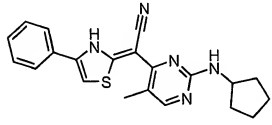
M^+(ES): 348.1; LC (215nm): 87.2%

Example 140: [2-(cyclopropylamino)pyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



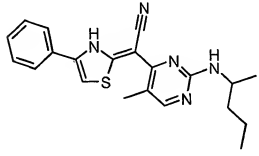
Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclopropylamine in the presence of triethylamine in DMA.
M^+(ES): 334.1; LC (215nm): 81%

Example 141: [2-(cyclopentylamino)-5-methylpyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



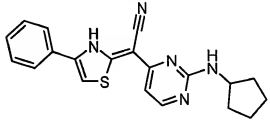
Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclopentylamine in the presence of triethylamine in DMA.
M^+(ES): 376.2; LC (215nm): 70%

Example 142: {5-methyl-2-[(1-methylbutyl)amino]pyrimidin-4-yl}(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



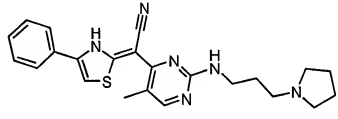
Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and (+/-)-2-aminopentane in the presence of triethylamine in DMA.
M^+(ES): 378.2; LC (215nm): 73.8%

Example 143: [2-(cyclopentylamino)pyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



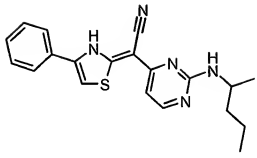
Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclopentylamine in the presence of triethylamine in DMA.
M^+(ES): 362.1; LC (215nm): 84.8%

Example 144: {5-methyl-2-[(3-pyrrolidin-1-ylpropyl)amino]pyrimidin-4-yl}(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



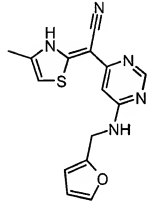
Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1-(3-aminopropyl)pyrrolidine in the presence of triethylamine in DMA.
M^+(ES): 419.2; LC (215nm): 88.9%

Example 145: {2-[(1-methylbutyl)amino]pyrimidin-4-yl}(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



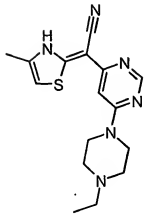
Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and (+/-)-2-aminopentane in the presence of triethylamine in DMA. M^+(ES): 364.1; LC (215nm): 79.2%

Example 146: {6-[(2-furylmethyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



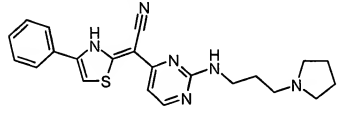
Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (6-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and furfurylamine in the presence of triethylamine in DMA. M^+(ES): 312.1; LC (215nm): 60.8%

Example 147: [6-(4-ethylpiperazin-1-yl)pyrimidin-4-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



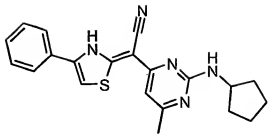
Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (6-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1-ethylpiperazine in the presence of triethylamine in DMA.
M^+(ES): 329.2; LC (215nm): 77.9%

Example 148: (4-phenyl-1,3-thiazol-2(3H)-ylidene){2-[(3-pyrrolidin-1-ylpropyl)amino]pyrimidin-4-yl}acetonitrile



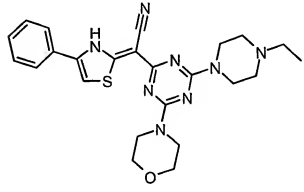
Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1-(3-aminopropyl)pyrrolidine in the presence of triethylamine in DMA.
M^+(ES): 405.2; LC (215nm): 82.2%

Example 149: [2-(cyclopentylamino)-6-methylpyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



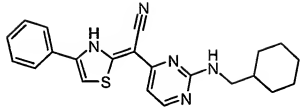
Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloro-6-methylpyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclopentylamine in the presence of triethylamine in DMA.
M^+(ES): 376.2; LC (215nm): 81.2%

Example 150: [4-(4-ethylpiperazin-1-yl)-6-morpholin-4-yl-1,3,5-triazin-2-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (4-chloro-6-morpholin-4-yl-1,3,5-triazin-2-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1-ethylpiperazine in the presence of triethylamine in DMA.
M^+(ES): 477.2; LC (215nm): 72.1%

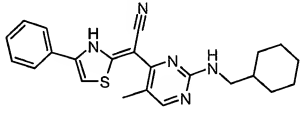
Example 151: {2-[(cyclohexylmethyl)amino]pyrimidin-4-yl}(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and (aminomethyl)cyclohexane in the presence of triethylamine in DMA.

M^+(ES): 390.2; LC (215nm): 96.4%

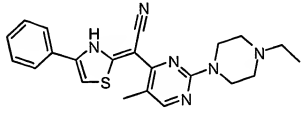
Example 152: {2-[(cyclohexylmethyl)amino]-5-methylpyrimidin-4-yl}(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and (aminomethyl)cyclohexane in the presence of triethylamine in DMA.

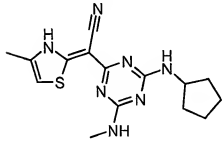
M^+(ES): 404.2; LC (215nm) : 84.6%

Example 153: [2-(4-ethylpiperazin-1-yl)-5-methylpyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



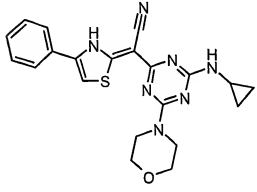
Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1-ethylpiperazine in the presence of triethylamine in DMA.
M^+(ES): 405.2; LC (215nm): 91.4%

Example 154: [4-(cyclopentylamino)-6-(methylamino)-1,3,5-triazin-2-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from [4-chloro-6-(methylamino)-1,3,5-triazin-2-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclopentylamine in the presence of triethylamine in DMA.
M^+(ES): 330.2; LC (215nm): 80.8%

Example 155: [4-(cyclopropylamino)-6-morpholin-4-yl-1,3,5-triazin-2-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

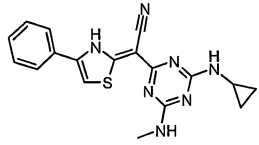


Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (4-chloro-6-morpholin-4-yl-1,3,5-triazin-2-yl)(4-phenyl-1,3-

thiazol-2(3H)-ylidene)acetonitrile and cyclopropylamine in the presence of triethylamine in DMA.

M^+(ES): 420.2; LC (215nm): 70.1%

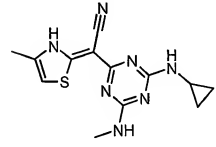
Example 156: [4-(cyclopropylamino)-6-(methylamino)-1,3,5-triazin-2-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from [4-chloro-6-(methylamino)-1,3,5-triazin-2-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclopropylamine in the presence of triethylamine in DMA.

M^+(ES): 364.1; LC (215nm): 91.6%

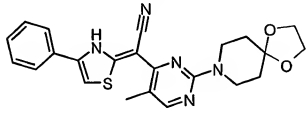
Example 157: [4-(cyclopropylamino)-6-(methylamino)-1,3,5-triazin-2-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from [4-chloro-6-(methylamino)-1,3,5-triazin-2-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclopropylamine in the presence of triethylamine in DMA.

M^+(ES): 302.1; LC (215nm): 94.2%

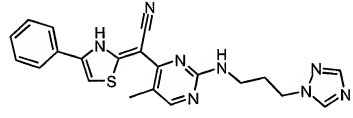
Example 158: [2-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-5-methylpyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1,4-dioxa-8-azaspiro[4.5]decane in the presence of triethylamine in DMA.

M^+(ES): 434.2; LC (215nm): 61.7%

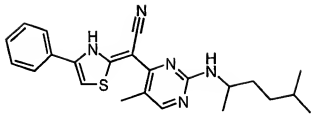
Example 159: (5-methyl-2-{[3-(1H-1,2,4-triazol-1-yl)propyl]amino}pyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1-(3'-aminopropyl)-1H-1,2,4-triazole in the presence of triethylamine in DMA.

M^+(ES): 417.2; LC (215nm): 78.2%

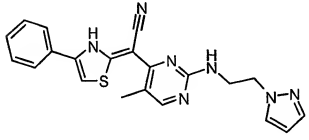
Example 160: {2-[(1,4-dimethylpentyl)amino]-5-methylpyrimidin-4-yl}(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1,4-dimethylpentylamine in the presence of triethylamine in DMA.

M^+(ES): 406.2; LC (215nm): 80.1%

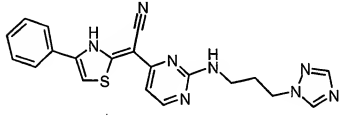
Example 161: (5-methyl-2-{[2-(1H-pyrazol-1-yl)ethyl]amino}pyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1-(2'-aminoethyl)pyrazole in the presence of triethylamine in DMA.

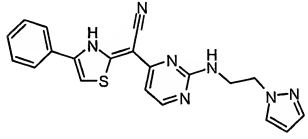
M^+(ES): 402.2; LC (215nm): 83.7%

Example 162: (4-phenyl-1,3-thiazol-2(3H)-ylidene)(2-{[3-(1H-1,2,4-triazol-1-yl)propyl]amino}pyrimidin-4-yl)acetonitrile



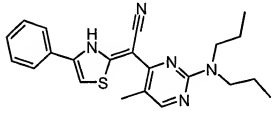
Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1-(3'-aminopropyl)-1H-1,2,4-triazole in the presence of triethylamine in DMA.
M^+(ES): 403.2; LC (215nm): 77.5%

Example 163: (4-phenyl-1,3-thiazol-2(3H)-ylidene)(2-{[2-(1H-pyrazol-1-yl)ethyl]amino}pyrimidin-4-yl)acetonitrile



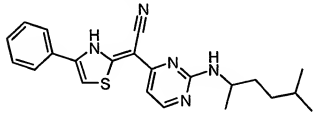
Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1-(2'-aminoethyl)pyrazole in the presence of triethylamine in DMA.
M^+(ES): 388.1; LC (215nm) : 78.8%

Example 164: [2-(dipropylamino)-5-methylpyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and dipropylamine in the presence of triethylamine in DMA.
M^+(ES): 392.2; LC (215nm): 74%

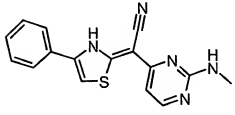
Example 165: {2-[(1,4-dimethylpentyl)amino]pyrimidin-4-yl}(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from from (2-chloropyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1,4-dimethylpentylamine in the presence of triethylamine in DMA.

M^+(ES): 392.2; LC (215nm): 68.9%

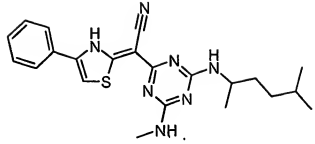
Example 166: [2-(methylamino)pyrimidin-4-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and methylamine in the presence of triethylamine in DMA.

M^+(ES): 308.1; LC (215nm): 68.3%

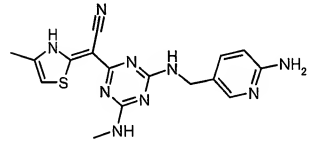
Example 167: [4-[(1,4-dimethylpentyl)amino]-6-(methylamino)-1,3,5-triazin-2-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from [4-chloro-6-(methylamino)-1,3,5-triazin-2-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1,4-dimethylpentylamine in the presence of triethylamine in DMA.

M^+(ES): 422.2; LC (215nm): 95.1%

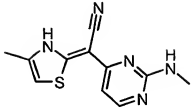
Example 168: [4-{[(6-aminopyridin-3-yl)methyl]amino}-6-(methylamino)-1,3,5-triazin-2-yl][(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from [4-chloro-6-(methylamino)-1,3,5-triazin-2-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 5-(aminomethyl)pyridin-2-amine in the presence of triethylamine in DMA.

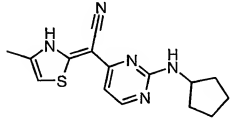
M^+(ES): 368.2; LC (215nm): 81.3%

Example 169: [2-(methylamino)pyrimidin-4-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



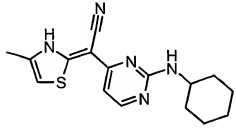
Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and methylamine in the presence of triethylamine in DMA. M^+(ES): 246.1; LC (215nm): 74.4%

Example 170: [2-(cyclopentylamino)pyrimidin-4-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



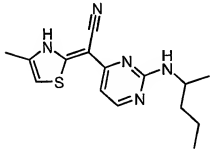
Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclopentylamine in the presence of triethylamine in DMA. M^+(ES): 300.2; LC (215nm): 81.1%

Example 171: [2-(cyclohexylamino)pyrimidin-4-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



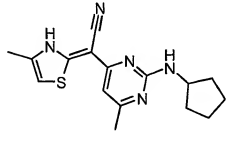
Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclohehylamine in the presence of triethylamine in DMA. M^+(ES): 314.1; LC (215nm): 64.7%

Example 172: {2-[(1-methylbutyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



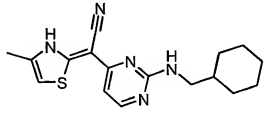
Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and (+/-)-2-aminopentane in the presence of triethylamine in DMA. M^+(ES): 302.2; LC (215nm): 72.7%

Example 173: [2-(cyclopentylamino)-6-methylpyrimidin-4-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloro-6-methylpyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and cyclopentylamine in the presence of triethylamine in DMA. M^+(ES): 314.2; LC (215nm): 84.6%

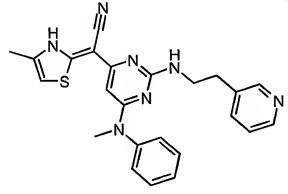
Example 174: {2-[(cyclohexylmethyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and (aminomethyl)cyclohexane in the presence of triethylamine in DMA.

M^+(ES): 328.2; LC (215nm): 76.6%

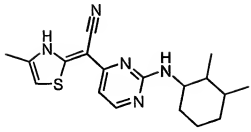
Example 175: {6-[methyl(phenyl)amino]-2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from {2-chloro-6-[methyl(phenyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 3-(2-aminoethyl)pyridine in the presence of triethylamine in DMA.

M^+(ES): 442.3; LC (215nm): 66.1%

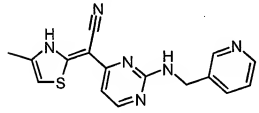
Example 176: {2-[(2,3-dimethylcyclohexyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 2,3-dimethylcyclohexylamine in the presence of triethylamine in DMA.

M^+(ES): 342.2; LC (215nm): 72.3%

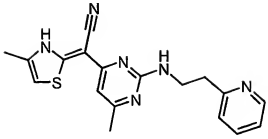
Example 177: (4-methyl-1,3-thiazol-2(3H)-ylidene){2-[(pyridin-3-ylmethyl)amino]pyrimidin-4-yl}acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrileand (3-aminomethyl)pyridine in the presence of triethylamine in DMA.

M^+(ES): 323.2; LC (215nm): 62%

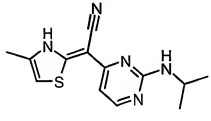
Example 178: {6-methyl-2-[(2-pyridin-2-ylethyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloro-6-methylpyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 2-(2-aminoethyl)pyridine in the presence of triethylamine in DMA.

M^+(ES): 351.2; LC (215nm): 73%

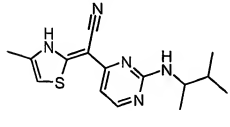
Example 179: [2-(isopropylamino)pyrimidin-4-yl](4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and iso-propylamine in the presence of triethylamine in DMA.

M^+(ES): 274.1; LC (215nm): 68.1%

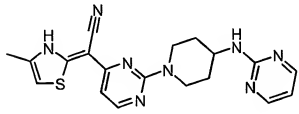
Example 180: {2-[(1,2-dimethylpropyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 1,2-dimethylpropylamine in the presence of triethylamine in DMA.

M^+(ES): 302.2; LC (215nm): 80.5%

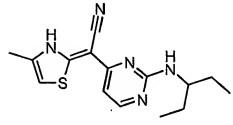
Example 181: (4-methyl-1,3-thiazol-2(3H)-ylidene){2-[4-(pyrimidin-2-ylamino)piperidin-1-yl]pyrimidin-4-yl}acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 2-(N-4-piperidinyl)-aminopyrimidine in the presence of triethylamine in DMA.

M^+(ES): 393.2; LC (215nm): 68.6%

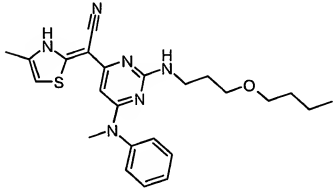
Example 182: {2-[(1-ethylpropyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 3-aminopentane in the presence of triethylamine in DMA.

M^+(ES): 302.2; LC (215nm): 75.5%

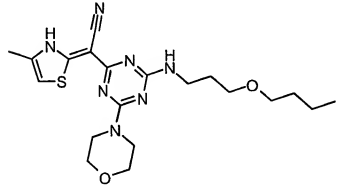
Example 183: {2-[(3-butoxypropyl)amino]-6-[methyl(phenyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from {2-chloro-6-[methyl(phenyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 3-butoxypropylamine in the presence of triethylamine in DMA.

M^+(ES): 451.3; LC (215nm): 85.7%

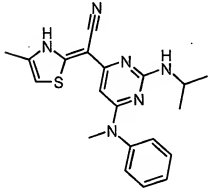
Example 184: {4-[(3-butoxypropyl)amino]-6-morpholin-4-yl-1,3,5-triazin-2-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (4-chloro-6-morpholin-4-yl-1,3,5-triazin-2-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 3-butoxypropylamine in the presence of triethylamine in DMA.

M^+(ES): 432.3; LC (215nm): 72.4%

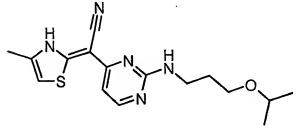
Example 185: {2-(isopropylamino)-6-[methyl(phenyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from {2-chloro-6-[methyl(phenyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and isopropylamine in the presence of triethylamine in DMA.

M^+(ES): 379.2; LC (215nm): 64.9%

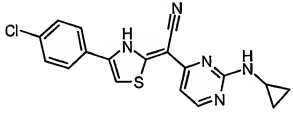
Example 186: {2-[(3-isopropoxypropyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile and 3-isopropoxypropylamine in the presence of triethylamine in DMA.

M^+(ES): 332.2; LC (215nm): 73.2%

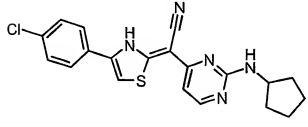
Example 187: [4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene][2-(cyclopropylamino)pyrimidin-4-yl]acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from [4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-chloropyrimidin-4-yl)acetonitrile and cyclopropylamine in the presence of triethylamine in DMA.

M^+(ES): 368.1; LC (215nm): 79.8%

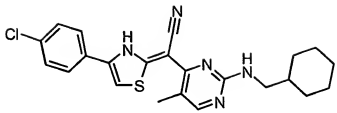
Example 188: [4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene][2-(cyclopentylamino)pyrimidin-4-yl]acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from [4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-chloropyrimidin-4-yl)acetonitrile and cyclopentylamine in the presence of triethylamine in DMA.

M^+(ES): 396.1; LC (215nm): 78.1%

Example 189: [4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene]{2-[(cyclohexylmethyl)amino]-5-methylpyrimidin-4-yl}acetonitrile



Following the general strategies and protocols outlined in the procedure J, the title compound was obtained from (2-chloro-5-methylpyrimidin-4-yl)[4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile and (aminoethyl)cyclohexane in the presence of triethylamine in DMA.
M^+(ES): 438.1; LC (215nm): 88.9%

Example 190 : Preparation of a pharmaceutical formulation

The following formulation examples illustrate representative pharmaceutical compositions according to the present invention being not restricted thereto.

Formulation 1 – Tablets
An azole compound of formula I is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ration. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 240-270 mg tablets (80-90 mg of active azole compound per tablet) in a tablet press.

Formulation 2 – Capsules
An azole compound of formula I is admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture is filled into 250 mg capsules (125 mg of active azole compound per capsule).

Formulation 3 – Liquid
An azole compound of formula I (1250 mg), sucrose (1.75 g) and xanthan gum (4 mg) are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously prepared solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89,

50 mg) in water. Sodium benzoate (10 mg), flavor, and color are diluted with water and added with stirring. Sufficient water is then added to produce a total volume of 5 mL.

Formulation 4 – Tablets

An azole compound of formula I is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 450-900 mg tablets (150-300 mg of active azole compound) in a tablet press.

Formulation 5 – Injection

An azole compound of formula (I) is dissolved in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/ml.

Biological Assays

The compounds of the present invention may be subjected to the following assays :

a) JNK2 and -3 in vitro assay:

The compounds of the present invention are inhibitors of JNKs. The phosphorylation of c-jun by JNK2 or JNK3 may be determined by monitoring the incorporation of ^{33}P into c-jun following the protocol below. The inhibitory activity of the compounds according to formula I, towards c-jun phosphorylation through JNK, is determined by calculating phosphorylation activity in the presence or absence of compounds according to formula I.

JNK3 and/or -2 assays are performed in 96 well MTT plates: incubation of 0.5 µg of recombinant, pre-activated GST-JNK3 or GST-JNK2 with 1 µg of recombinant, biotinylated GST-c-Jun and 2 µM $^{33}\gamma$-ATP (2 nCi/µl), in the presence or absence of compounds according to formula I and in a reaction volume of 50 µl containing 50 mM Tris-HCl, pH 8.0; 10 mM $MgCl_2$; 1 mM Dithiothreitol, and 100 µM $NaVO_4$. The test compound according to formula I is used in concentrations of 10, 3, 033, 0.1, 0.033, 0.01, 0.0033, 0.001 µM. The incubation is performed for 120 min. at R.T and stopped upon addition of 200 µl of a solution containing 250 µg of Streptavidine-coated SPA beads (Amersham, Inc.)*, 5 mM EDTA, 0.1% Triton X-100 and 50 µM ATP, in phosphate saline buffer.

After incubation for 60 minutes at RT, beads are sedimented by centrifugation at 1500 x g for 5 minutes, resuspended in 200 µl of PBS containing 5 mM EDTA, 0.1% Triton X-100 and 50 µM ATP and the radioactivity measured in a scintillation β counter, following sedimentation of the beads as described above.

The tested compounds according to formula I display an inhibition (IC_{50}) with regard to JNK3 of less than 20 μM, preferably less than 1 μM.

b) GSK3 in vitro assay:

GSK3β Assay (see Naerum et al., *Bioorg. Med. Chem. Lett* **12** p.1525-1528 (2002))

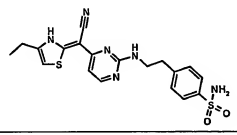
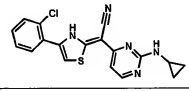
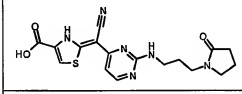
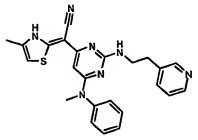
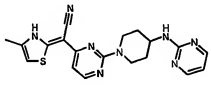
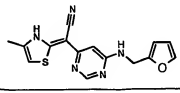
In a final reaction volume of 25μl, the protein kinase GSK3β (h) (5-10mU) is incubated with 8 mM MOPS at a pH of 7.0, in 0.2 mM EDTA, as well as 20μM of the peptide YRRAAVPPSPSLSRHSSPHQS(p)EDEEE (a phospho GS2 peptide being the GSK3 substratein this assay), 10mM Mg Acetate and [γ-^{33}P-ATP] (Specific activity approx. 500cpm/pmol, concentration as required). The reaction is initiated by the addition of Mg^{2+} [γ-^{33}P-ATP]. The test compound according to formula I is used in concentrations of 100, 25, 5, 1.25, 0.315, 0.078, 0.0195, 0.0049, 0.0012, 0.00031 μM. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 5μl of a 3% phosphoric acid solution. 10μl of the reaction is then spotted onto a P30 filtermat and washed three times for 5 minutes in 50mM phosphoric acid and once in methanol prior to drying and the degree of phosphorylation of the substrate is determined by scintillation counting.

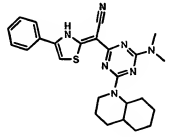
The tested compounds according to formula I display an inhibition (IC_{50}) with regard to GSK3 of less than 20 μM, preferably less than 10 and even more preferred less than 1 μM.

The binding affinities of the compounds of formula (I) were assessed using the above described *in vitro* biological assay. Representative values for some example compounds are given in Tables 1 and 2 below.

The values in Table 1 refer to the binding affinity (IC_{50}; μM) of the example compounds according to formula I to GSK3.

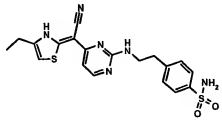
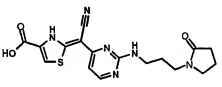
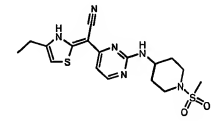
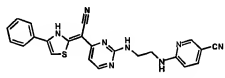
Table 1: In vitro potency of azole derivatives on human GSK3 β

Structure	Compound	IC_{50} (μM) GSK3β
	4-[2-({4-[cyano(4-ethyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)ethyl]benzenesulfonamide	<10
	[4-(2-chlorophenyl)-1,3-thiazol-2(3H)-ylidene][2-(cyclopropylamino)pyrimidin-4-yl]acetonitrile	<10
	2-[cyano(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)methylene]-2,3-dihydro-1,3-thiazole-4-carboxylic acid	<10
	{6-[methyl(phenyl)amino]-2-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile	<10
	(4-methyl-1,3-thiazol-2(3H)-ylidene){2-[4-(pyrimidin-2-ylamino)piperidin-1-yl]pyrimidin-4-yl}acetonitrile	<10
	{6-[(2-furylmethyl)amino]pyrimidin-4-yl}(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile	<10

	[4-(dimethylamino)-6-(octahydroquinolin-1(2H)-yl)-1,3,5-triazin-2-yl](4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile	<10

The values in Table 2 refer to the binding affinity (IC_{50}; μM) of the example compounds according to formula I to JNK3.

Table 2 In vitro potency of azole derivatives on rat JNK3

Structure	IUPAC-Name	JNK3 IC50 (μM)
	4-[2-({4-[cyano(4-ethyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)ethyl]benzenesulfonamide	<10
	2-[cyano(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}pyrimidin-4-yl)methylene]-2,3-dihydro-1,3-thiazole-4-carboxylic acid	<10
	(4-ethyl-1,3-thiazol-2(3H)-ylidene)(2-{[1-(methylsulfonyl)piperidin-4-yl]amino}pyrimidin-4-yl)acetonitrile trifluoroacetate	<10
	6-{[2-({4-[cyano(4-phenyl-1,3-thiazol-2(3H)-ylidene)methyl]pyrimidin-2-yl}amino)ethyl]amino}nicotinonitrile	<10

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